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Gaster et al.

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[54] **PENTACYCLIC COMPOUNDS**

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[22] Filed: **Dec. 20, 1984**

Related U.S. Application Data

[62] Division of Ser. No. 472,218, Mar. 4, 1983, Pat. No. 4,504,480.

[30] **Foreign Application Priority Data**

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[52] **U.S. Cl.** ..... **260/239 D**; 260/239 BD; 260/243.3; 260/245.5; 514/214

[58] **Field of Search** ..... 260/239 D, 243.3, 239 BD

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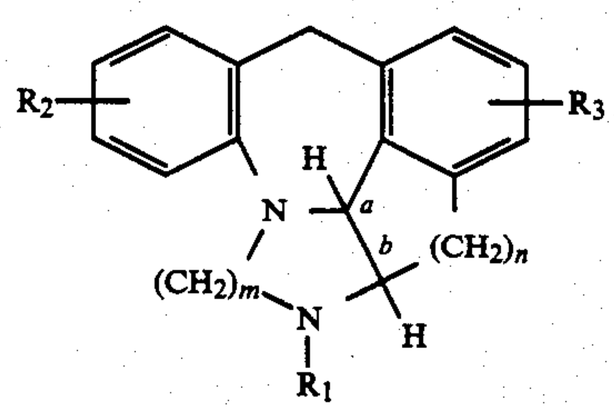
[57] **ABSTRACT**

Compounds of formula (I),



(I)

or an N-oxide or pharmaceutically acceptable salt thereof, wherein R_1 is hydrogen, C_{1-7} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl or C_{1-4} alkyl substituted by C_{2-7} alkenyl, C_{2-7} alkynyl, C_{3-7} cycloalkyl, hydroxy, thiol, C_{1-4} alkoxy, C_{1-4} alkylthio, carboxy, C_{1-4} alkoxycarbonyl, C_{1-4} alkanoyl, amino optionally substituted by one or two C_{1-4} alkyl or by C_{4-6} polymethylene optionally containing an oxygen or nitrogen atom, aminocarbonyl optionally N-substituted by one or two C_{1-4} alkyl, or benzoyl or phenyl either being optionally ring-substituted by C_{1-4} *alkyl,* C_{1-4} alkoxy, halogen or trifluoromethyl, R_2 and R_3 are the same or different and are hydrogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, halogen or trifluoromethyl, m is 1 to 3 and n is 1 or 2, the hydrogen atom bonded to the C_a carbon atom being trans to the hydrogen atom bonded to the C_b carbon atom, having mood-modifying activity such as anti-depressant activity.

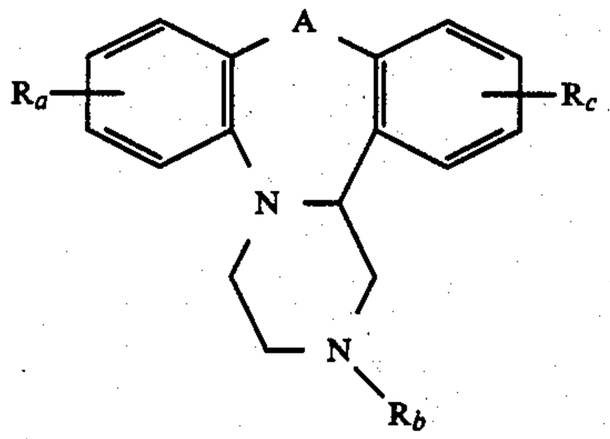
2 Claims, No Drawings

PENTACYCLIC COMPOUNDS

This application is a division of co-pending U.S. patent application Ser. No. 472,218, filed Mar. 4, 1983, now U.S. Pat. No. 4,504,480.

This invention relates to novel pentacyclic compounds having pharmacological activity, to processes and intermediates of use in their preparation, to pharmaceutical compositions containing them, and to their use in the treatment of mammals.

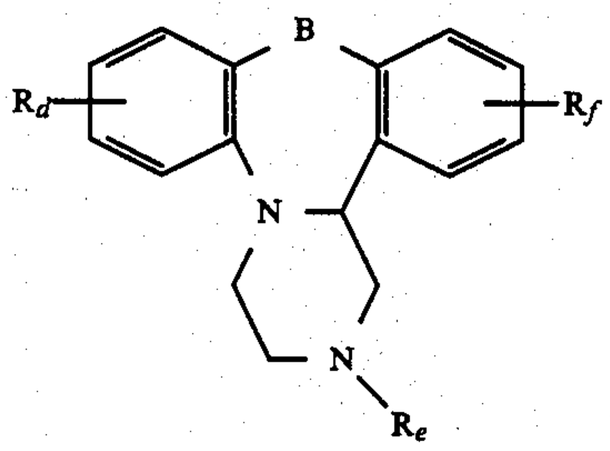
U.K. Pat. No. 1,173,783 discloses compounds of formula (A);



(A)

wherein R_a and R_c each represent a hydrogen or halogen atom, a hydroxy, lower acyloxy, alkyl or alkoxy group, or a trifluoromethyl group, R_b represents hydrogen, a lower alkyl or aralkyl group, an aminoethyl or aminopropyl group N-substituted by one or more lower alkyl groups, or a lower alkyl group forming a substituent of an N-containing heterocyclic ring, the said ring being directly bonded to the nitrogen atom of the piperazine ring, and A represents a single bond, or a methylene, ethylene or —CH=CH— group.

U.K. Pat. No. 1,229,252 discloses compounds of formula (B);

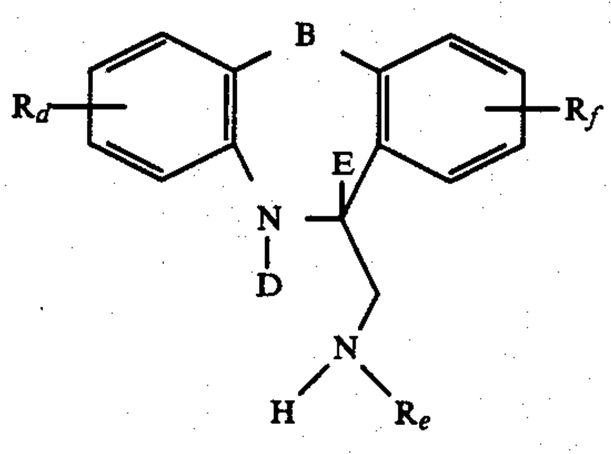


(B)

wherein R_d and R_f represent hydrogen, halogen, hydroxy, acyloxy, lower alkoxy or lower alkyl or trifluoromethyl, R_e represents hydrogen, lower alkyl, lower aralkyl, aminoethyl or aminopropyl optionally N-substituted by lower alkyl, or lower alkyl substituted by a nitrogen-containing heterocyclic ring, and B represents oxygen, sulphur, or NRg, Rg representing lower alkyl.

The compounds of formulae (A) and (B) are disclosed as having anti-inflammatory, anti-serotoninic, anti-histaminic, anti-phlogistic and cardiovascular activities. In addition, the compound of formula (A), wherein R_a and R_c are both hydrogen, R_b is methyl and A is methylene, is commonly known as mianserin and is marketed as an anti-depressant agent for the treatment of depression in mammals.

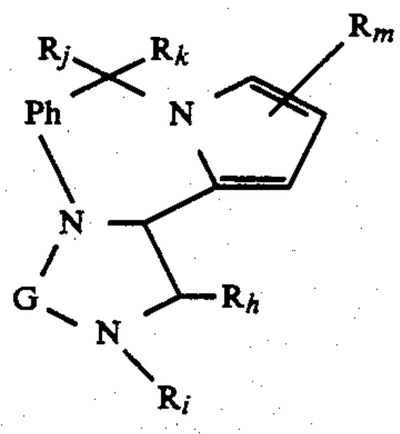
U.K. Pat. No. 1,229,253 discloses compounds of formula (C);



(C)

wherein R_d, R_e, R_f and B are as defined in relation to formula (B) above, and D and E are either hydrogen or together represent a double bond between the nitrogen and carbon atoms to which they are attached, and functional derivatives thereof. Such compounds are disclosed as having sedative, tranquilising and anti-depressant activity.

U.S. Pat. No. 4,316,900 discloses compounds of formula (D);



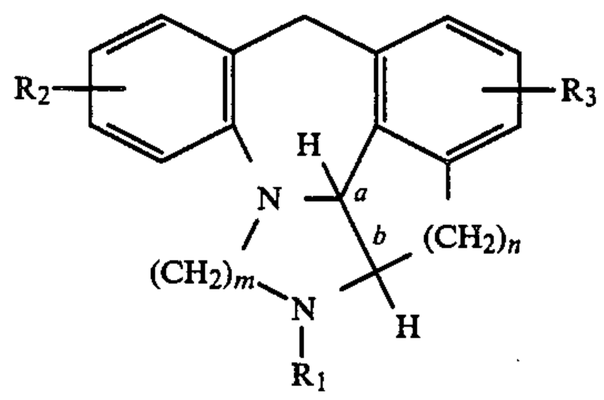
(D)

and salts thereof derived from pharmaceutically acceptable acids or ammonium or alkali metal bases, wherein R_h, R_j and R_k are each hydrogen or lower alkyl, R_i is hydrogen, lower or higher alkyl, lower alkenyl, lower alkynyl, C_{3-7} cycloalkyl, cycloalkenyl or lower alkyl substituted by cycloalkyl, hydroxy, amino, mono- or di-lower alkylamino, carboxy, lower carbalkoxy, carbamoyl, mono- or di-lower alkyl carbamoyl, phenyl, lower alkanoyl or benzoyl, Ph is 1,2-phenylene unsubstituted or substituted by up to two members selected from lower alkyl, lower alkoxy, lower alkylthio, halogen and trifluoromethyl, G is lower alkylene separating both nitrogen atoms by 2 or 3 carbon atoms and R_m is hydrogen, lower alkyl, carboxy, lower carbalkoxy or lower alkyl substituted by hydroxy, amino, mono- or di-lower alkylamino, and the lower alkoxycarbonyl, lower or higher alkanoyl, adamantoyl, carbamoyl, mono- or di-lower alkylcarbamoyl, C_{3-7} cycloalkylcarbonyl or benzoyl derivatives thereof, and the 2-N-oxide, 2-lower alkyl or 2-phenyl lower alkyl quaternaries and salts thereof derived from pharmaceutically acceptable acids or bases. Such compounds are described as anti-depressant agents suitable, for example, in the treatment or management of mental depression in mammals.

A structurally distinct class of compounds has now been discovered which compounds are dibenz[b,e]azepines in which the azepine nitrogen atom and the azepine carbon atom adjacent thereto are joined with C_{1-3} alkyleneaminomethylene to form a 5- to 7-membered ring, characterised by a methylene or ethylene bridge from the carbon atom of the aminomethylene moiety to the carbon atom of the benzo moiety that is in the ortho-position to the azepine ring and that is on the same side as, and three carbon's distance from, the azepine nitrogen atom, the bridge thus forming a 5- or 6-membered

ring. Such compounds, moreover, have been found to have pharmacological activity, in particular mood-modifying activity, such as anti-depressant activity.

Accordingly, the present invention provides a compound of formula (I);



(I)

or an N-oxide or pharmaceutically acceptable salt thereof, wherein R_1 is hydrogen, C_{1-7} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl or C_{1-4} alkyl substituted by C_{2-7} alkenyl, C_{2-7} alkynyl, C_{3-7} cycloalkyl, hydroxy, thiol, C_{1-4} alkoxy, C_{1-4} alkylthio, carboxy, C_{1-4} alkoxycarbonyl, C_{1-4} alkanoyl, amino optionally substituted by one or two C_{1-4} alkyl or by C_{4-6} polymethylene optionally containing an oxygen or nitrogen atom, aminocarbonyl optionally N-substituted by one or two C_{1-4} alkyl, or benzoyl or phenyl either being optionally ring-substituted by C_{1-4} alkyl, C_{1-4} alkoxy, halogen or trifluoromethyl, R_2 and R_3 are the same or different and are hydrogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, halogen or trifluoromethyl, m is 1 to 3 and n is 1 or 2, the hydrogen atom bonded to the C_a carbon atom being trans to the hydrogen atom bonded to the C_b carbon atom.

Within the definition for R_1 is a sub-group, wherein R_1 is hydrogen, C_{1-4} alkyl, C_{1-4} alkyl substituted by amino optionally substituted by one or two C_{1-4} alkyl or by C_{4-6} polymethylene optionally containing an oxygen or nitrogen atom, or C_{1-4} alkyl substituted by phenyl optionally substituted by C_{1-4} alkyl, C_{1-4} alkoxy, halogen or trifluoromethyl.

When R_1 is C_{1-4} alkyl substituted by phenyl optionally substituted as hereinbefore defined, examples of such optional substituents include methyl, ethyl, methoxy, ethoxy, fluoro, chloro, bromo or trifluoromethyl. Preferably, phenyl is unsubstituted.

When R_1 is C_{1-4} alkyl substituted by amino optionally substituted as hereinbefore defined, examples of such optional substituents include methyl and ethyl and, together with the nitrogen atom, piperidino and morpholino.

Preferably, R_1 is hydrogen or C_{1-4} alkyl, in particular C_{1-4} alkyl, such as methyl and ethyl.

Within the definition for R_2 and R_3 is a sub-group, wherein R_2 and R_3 are the same or different and are hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy, halogen or trifluoromethyl.

Preferred examples for R_2 and R_3 are hydrogen, hydroxy, methyl, ethyl, methoxy, ethoxy, bromo, chloro, fluoro and trifluoromethyl. Preferably, R_2 is hydrogen, methoxy, hydroxy, methyl or chloro and R_3 is hydrogen.

Preferably, m is 1 or 2.

Preferably, n is 1.

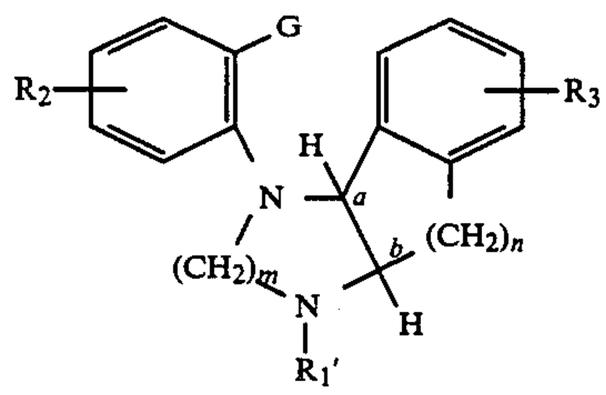
The compounds of the invention have chiral centres at the C_a and C_b carbon atoms and therefore can exist in enantiomeric forms. The present invention extends to such enantiomers individually and as mixtures including racemates.

Particularly preferred compounds within formula (I) are the compounds of the examples described hereinafter or an N-oxide or pharmaceutically acceptable salt thereof. The most preferred compound of formula (I) is trans-12-methyl-1,10,11,12,12a, 12b-hexahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]fluorene, which is the compound prepared in Example 1, or an N-oxide or pharmaceutically acceptable salt thereof.

An N-oxide of a compound of formula (I) includes the oxide of either nitrogen atom shown in formula (I) and the oxide of any nitrogen-containing substituent for R_1.

A pharmaceutically acceptable salt of a compound of formula (I) includes an acid addition salt of either nitrogen atom shown in formula (I) and of any nitrogen-containing substituent for R_1, the acid addition salt being derived from a pharmaceutically acceptable inorganic or organic acid, such as hydrochloric acid, hydrobromic acid, sulphuric acid, maleic acid and acetic acid. A pharmaceutically acceptable salt of a compound of formula (I) also includes alkali metal or alkaline earth metal salts of any carboxy-containing substituent for R_1. Examples of such salts include potassium, sodium, calcium and magnesium salts.

The present invention also provides a process for preparing a compound of formula (I), as defined hereinbefore, which comprises cyclising a compound of formula (II);



(II)

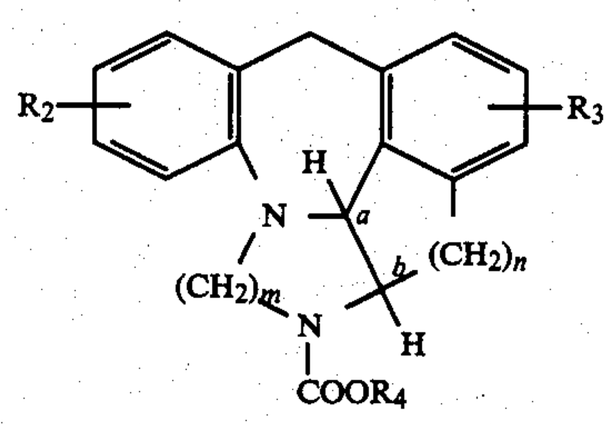
wherein R_2, R_3, m, n and the configuration of the C_a and C_b hydrogen atoms are as defined hereinbefore, R_1' is R_1 or C_{1-4} alkoxycarbonyl, phenoxycarbonyl or benzyloxycarbonyl and G is formyl, carboxy or a C_{1-4} alkyl ester thereof or is CH_2L_1, L_1 being a leaving group; in the case when R_1' is C_{1-4} alkoxycarbonyl, phenoxycarbonyl or benzyloxycarbonyl, converting R_1' into R_1; in the case when G is formyl, carboxy or a C_{1-4} alkyl ester thereof, reducing the resulting carbonyl or hydroxymethylene moiety to a methylene moiety; optionally converting R_1, R_2 or R_3 in the resulting compound of formula (I) into another R_1, R_2 or R_3; and optionally forming an N-oxide or pharmaceutically acceptable salt thereof.

Preferred examples of the leaving group (L_1) include hydroxy, bromo, chloro, C_{1-4} alkoxy, C_{1-4} alkanoyloxy, C_{1-4} alkoxycarbonyloxy, tosyloxy and mesyloxy.

When the leaving group (L_1) is hydroxy, C_{1-4} alkoxy, C_{1-4} alkanoyloxy, C_{1-4} alkoxycarbonyloxy, tosyloxy or mesyloxy, or when G is formyl, carboxy or a C_{1-4} alkyl ester thereof, the cyclisation reaction is preferably carried out in the presence of a dehydrating agent, for example orthophosphoric acid or methane sulphonic acid containing phosphorus pentoxide.

When the leaving group (L_1) is bromo or chloro, the cyclisation reaction is preferably carried out in the presence of a Lewis acid, such as aluminium trichloride.

When R_1' is C_{1-4} alkoxycarbonyl, pheoxycarbonyl or benzyloxycarbonyl, the process proceeds through an intermediate of formula (III);

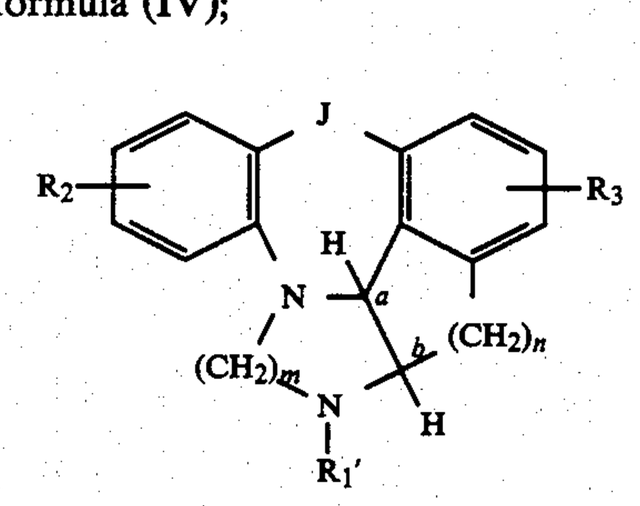


(III)

wherein R_2, R_3, m, n and the configuration of the C_a and C_b hydrogen atoms are as defined hereinbefore and R_4 is C_{1-4} alkyl, phenyl or benzyl.

The conversion of the C_{1-4} alkoxycarbonyl, phenoxycarbonyl or benzyloxycarbonyl group into R_1 may be carried out in accordance with any appropriate known procedure. For example, the group may be hydrolysed with concomitant decarboxylation using ethanolic sodium hyroxide to give a compound of formula (I), wherein R_1 is hydrogen, which may then optionally be converted into another R_1, as described hereinafter. Alternatively, the group may be reduced using, for example, lithium aluminium hydride in a solvent, for example, ether or tetrahydrofuran, to give a compound of formula (I), wherein R_1 is methyl.

When G is formyl, carboxy or a C_{1-4} alkyl ester thereof, the process proceeds through an intermediate of formula (IV);



(IV)

wherein R_1', R_2, R_3, m, n and the configuration of the C_a and C_b hydrogen atoms are as defined hereinbefore and J is CO or CHOH, when G in formula (II) is carboxy or a C_{1-4} alkyl ester thereof, or is CHOH, when G in formula (II) is formyl.

The reduction of the resulting carbonyl or hydroxymethylene moiety may be carried out using, for example, catalytic hydrogenation.

Examples of an optional conversion of R_1 in a compound of formula (I) into another R_1 include the conversion of C_{1-4} alkyl substituted by hydroxy into C_{1-4} alkyl substituted by thiol by, for example, first forming a C_{1-4} alkyl halide, such as the chloride, and then reacting the C_{1-4} alkyl halide with potassium hydrogen sulphide, or into C_{1-4} alkyl substituted by C_{1-4} alkoxy using, for example, sodium hydride and a C_{1-4} alkyl halide; the conversion of C_{1-4} alkyl substituted by thiol into C_{1-4} alkyl substituted by C_{1-4} alkylthio using, for example, a base and a C_{1-4} alkyl halide; the conversion of C_{1-4} alkyl substituted by C_{1-4} alkoxycarbonyl into C_{1-4} alkyl substituted by carboxy by hydrolysis; the conversion of C_{1-4} alkyl substituted by carboxy into C_{1-4} alkyl substituted by aminocarbonyl optionally N-substituted by one or two C_{1-4} alkyl by, for example, first forming the carboxylic acid halide, such as the chloride, and then reacting the acid halide with ammonia optionally substituted by one or two C_{1-4} alkyl; and the conversion of C_{1-3} alkyl substituted by aminocarbonyl optionally N-substituted by one or two C_{1-4} alkyl into C_{1-4} alkyl substituted by amino optionally substituted by one or two C_{1-4} alkyl by reduction.

An important sub-class of an optional conversion of R_1 is that in which a compound of formula (I), wherein R_1 is hydrogen, is converted into another compound of formula (I), wherein R_1 is as follows:

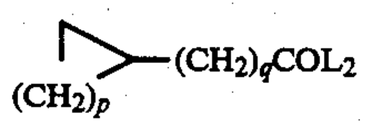
(a) wherein R_1 is C_{1-7} alkyl, by alkylation with a C_{1-7} alkyl halide in a solvent, such as acetone, in the presence of a base, or by reductive C_{1-7} alkylation in which a mixture of a compound of formula (I), wherein R_1 is hydrogen, and a C_{1-7} aldehyde is reduced catalytically or with sodium cyanoborohydride in a solvent, such as ethanol, or by C_{2-7} acylation using a carboxylic acid chloride or anhydride in a solvent, such as methylene dichloride, in the presence of an organic or inorganic base, for example pyridine, triethylamine or potassium carbonate, and then reduction of the C_{2-7} acylated derivative with, for example, lithium aluminium hydride;

(b) wherein R_1 is C_{3-7} cycloalkyl, by reductive alkylation, as described in paragraph (a), using a C_{3-7} cycloalkanone;

(c) wherein R_1 is C_{3-7} cycloalkenyl, by reaction with a C_{3-7} cycloalkenyl halide, such as a C_{3-7} cycloalkenyl bromide, when the halide atom is allylic, or by reductive alkylation, as described in paragraph (a), using a C_{3-7} cycloalkenone;

(d) wherein R_1 is C_{1-4} alkyl substituted by C_{2-7} alkenyl or C_{2-7} alkynyl, by reaction with a C_{2-11} alkenyl or C_{2-11} alkynyl halide, such as a C_{2-11} alkenyl or C_{2-11} alkynyl bromide, in a solvent, such as acetone, in the presence of a base, such as potassium carbonate;

(e) wherein R_1 is C_{1-4} alkyl substituted by C_{3-7} cycloalkyl, by acylation with a compound of formula (V);



(V)

in which p is 1 to 5, q is 0 to 3 and L_2 is a leaving group, such as chloro, and then reduction of the acylated derivative, as described in paragraph (a);

(f) wherein R_1 is C_{1-4} alkyl substituted by hydroxy, by reaction with aqueous formaldehyde when R_1 is hydroxymethyl, by reaction with ethylene oxide when R_1 is hydroxyethyl, or by Michael addition with ethyl acrylate or by reaction with ethyl ω-bromobutyrate and reduction of the ester with lithium aluminium hydride when R_1 is respectively hydroxypropyl or hydroxybutyl;

(g) wherein R_1 is C_{1-4} alkyl substituted by C_{1-4} alkoxycarbonyl, by reaction with a compound of formula (VI);

$$L_3—(CH_2)_r—CO_2R_5 \qquad (VI)$$

in which R_5 is C_{1-4} alkyl, L_3 is a leaving group, such as bromo, and r is 1 to 4, in a solvent, such as methylene dichloride, in the presence of a base, or by Michael addition with a C_{1-4} alkyl acrylate when R_1 is ethyl substituted by C_{1-4} alkoxycarbonyl;

(h) wherein R_1 is C_{1-4} alkyl substituted by C_{1-4} alkanoyl, by reaction with a C_{1-4} alkanoyl C_{1-4} alkyl halide or by Michael addition with a C_{1-4} alkyl vinyl ketone when R_1 is ethyl substituted by C_{1-4} alkanoyl;

(i) wherein R_1 is C_{1-4} alkyl substituted by amino optionally substituted by one or two C_{1-4} alkyl or by C_{4-6} polymethylene optionally containing an oxygen or nitrogen atom, by reaction with a compound of formula (VII);

$$L_4—(CH_2)_r—NR_6R_7 \quad (VII)$$

in which R_6 and R_7 are hydrogen or C_{1-4} alkyl or together are C_{4-6} polymethylene optionally containing an oxygen or nitrogen atom, L_4 is a leaving group, such as chloro, and r is as hereinbefore defined, in a solvent, such as acetone, in the presence of a base, or by reaction with bromoacetyl bromide, reaction with HNR_6R_7, R_6 and R_7 being as defined hereinbefore, and then reduction, as described in paragraph (a), when R_1 is ethyl substituted by amino optionally substituted by one or two C_{1-4} alkyl or by C_{4-6} polymethylene optionally containing an oxygen or nitrogen atom;

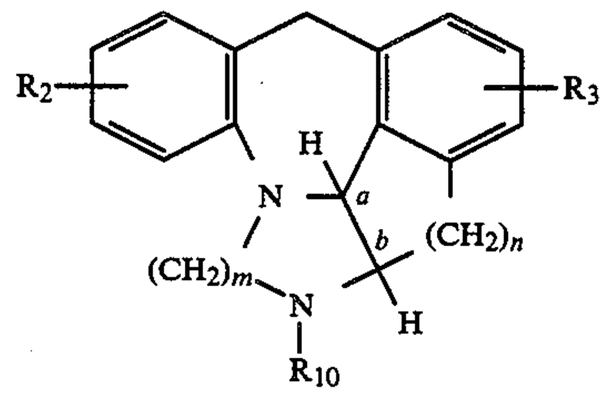
(j) wherein R_1 is C_{1-4} alkyl substituted by aminocarbonyl optionally N-substituted by one or two C_{1-4} alkyl, by reaction with a compound of formula (VIII);

$$L_5—(CH_2)_r—CO—NR_8R_9 \quad (VIII)$$

in which L_5 is a leaving group, such as halide, in particular bromide, r is as hereinbefore defined and R_8 and R_9 are hydrogen or C_{1-4} alkyl;

(k) wherein R_1 is C_{1-4} alkyl substituted by benzoyl or phenyl either being optionally substituted by C_{1-4} alkyl, C_{1-4} alkoxy, halogen or trifluoromethyl, by reaction with the correspondingly substituted C_{1-4} alkyl halide, such as the bromide.

The present invention extends to all of the above conversions, whether singly or in combination, and to the intermediates used therein, which together are of formula (IX);



(IX)

wherein R_2, R_3, m, n and the configuration of the C_a and C_b hydrogen atoms are as defined hereinbefore and R_{10} is C_{1-4} alkyl substituted by halogen or halocarbonyl or is C_{1-4} alkylcarbonyl, C_{3-7} cycloalkylcarbonyl, C_{3-7} cycloalkyl C_{1-3} alkylcarbonyl or halo C_{1-4} alkylcarbonyl.

When R_1 in formula (II) is a functional group that may possibly interfere with the course of the reaction or that may not possibly survive it, then it is preferred to carry out the preparation of a compound of formula (I) with R_1 as hydrogen and subsequently to convert the hydrogen atom into the desired group for R_1 by, for example, one or more of the conversions described hereinbefore.

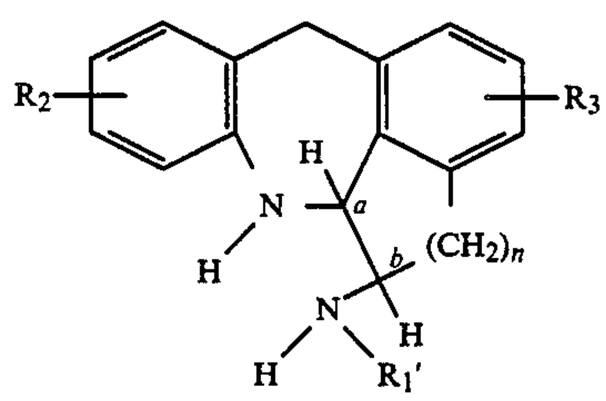
An example of an optional conversion of R_2 or R_3 in a compound of formula (I) into another R_2 or R_3 is the conversion of C_{1-4} alkoxy into hydroxy using, for example, aqueous hydrobromic acid.

The optional formation of an N-oxide may be carried out by reacting a compound of formula (I) with an organic peracid, such as m-chloroperbenzoic acid.

The optional formation of a pharmaceutically acceptable acid addition salt of a compound of formula (I) may be carried out by simple reaction of a compound of formula (I) with a pharmaceutically acceptable acid.

The optional formation of a pharmaceutically acceptable alkali or alkaline earth metal salt of a compound of formula (I), wherein R_1 is a carboxy-containing substituent, may be carried out by reaction of a compound of formula (I) with an alkali or alkaline earth metal or the hydroxide thereof.

The present invention provides a second process for preparing a compound of formula (I), as defined hereinbefore, which comprises reacting a compound of formula (X);



(X)

wherein R_1', R_2, R_3, n and the configuration of the C_a and C_b hydrogen atoms are as defined hereinbefore, with a compound of formula (XI);

$$L_7—(CO)_s—(CH_2)_t—(CO)_u—L_8 \quad (XI)$$

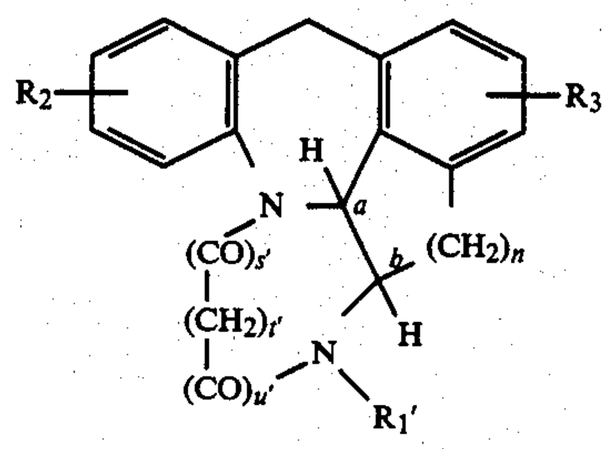
wherein L_7 and L_8 are leaving groups, s and u are 0 or 1 and t is 0 to 3 such that s+t+u is 1 to 3; in the case when s or u is 1, reducing the carbonyl moiety to give a methylene moiety; in the case when R_1' is C_{1-4} alkoxycarbonyl, phenoxycarbonyl or benzyloxycarbonyl, converting R_1' into R_1; optionally converting R_1, R_2 or R_3 in the resulting compound of formula (I) into another R_1, R_2 or R_3; and optionally forming an N-oxide or pharmaceutically acceptable salt thereof.

Preferred examples of the leaving groups (L_7 and L_8) include halo, such as chloro and bromo, C_{1-4} alkoxy, and labile acyloxy, such as mesyloxy and tosyloxy.

Preferred examples of a compound of formula (XI) include diethyl oxalate, bromoacetyl bromide, methyl bromoacetate, dibromoethane, oxalyl chloride and phosgene. Apart from diethyl oxalate which is used neat, all these compounds are reacted with a compound of formula (X), when R_1' is other than C_{1-4} alkoxycarbonyl, phenoxycarbonyl or benzyloxycarbonyl, in a solvent, for example, benzene, toluene, methylene dichloride, dimethyl sulphoxide or diethyl ether, in the presence of an organic or inorganic base, for example triethylamine, pyridine, picoline or potassium carbonate. On the other hand, when R_1' is C_{1-4} alkoxycarbonyl, phenoxycarbonyl or benzyloxycarbonyl, the reaction at the carbamate nitrogen requires a solvent, such as dimethylformamide, and the presence of a strong base, such as sodium hydride.

When s or u is 1, the process proceeds through an intermediate of formula (XII);

(XII)



wherein R_1', R_2, R_3, n and the configuration of the C_a and C_b hydrogen atoms are as defined hereinbefore and s', t' and u' respectively are the same as s, t and u, as defined hereinbefore, with the proviso that at least one of s and u is 1.

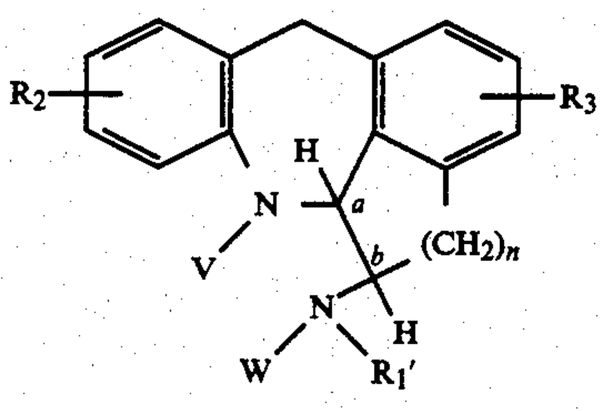
The reduction of the carbonyl moiety to give a methylene moiety is preferably carried out with diborane or lithium aluminium hydride.

When m in formula (I) is 2 or 3, however, s and u are preferably 0, thus avoiding the need for an additional reduction step.

The conversion of R_1', when C_{1-4} alkoxycarbonyl, phenoxycarbonyl or benzyloxycarbonyl, into R_1, the optional conversion of R_1, R_2 or R_3 in the resulting compound of formula (I) into another R_1, R_2 or R_3, and the optional formation of an N-oxide or pharmaceutically acceptable salt may be carried out as described hereinbefore.

The present invention provides a third process for preparing a compound of formula (I), wherein m is 2, which comprises cyclising a compound of formula (XIII);

(XIII)



wherein R_1', R_2, R_3, n and the configuration of the C_a and C_b hydrogen atoms are as defined hereinbefore and one of V and W is hydrogen and the other is $(CH_2)_2L_9$, L_9 being a leaving group; in the case when R_1' is C_{1-4} alkoxycarbonyl, phenoxycarbonyl or benzyloxycarbonyl, converting R_1' into R_1; optionally converting R_1, R_2 or R_3 in the resulting compound of formula (I) into another R_1, R_2 or R_3; and optionally forming an N-oxide or pharmaceutically acceptable salt thereof.

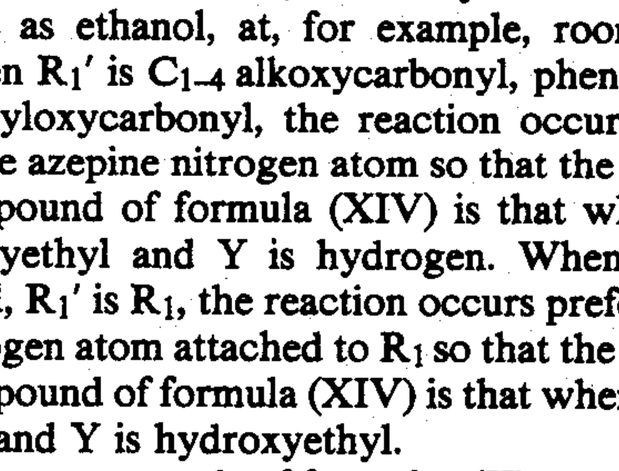
Preferred examples of the leaving group (L_9) include halo, such as chloro and bromo, and labile acyloxy, such as mesyloxy and tosyloxy.

The cyclisation may be carried out in a solvent in the presence of a base, as described hereinbefore for the reaction between compounds of formulae (X) and (XI).

The conversion of R_1', when C_{1-4} alkoxycarbonyl phenoxycarbonyl or benzyloxycarbonyl, into R_1, the optional conversion of R_1, R_2 or R_3 in the resulting compound of formula (I) into another R_1, R_2 or R_3, and the optional formation of an N-oxide or pharmaceutically acceptable salt may be carried out as described hereinbefore.

The compound of formula (XIII) may be prepared by converting the hydroxy moiety in a compound of formula (XIV);

(XIV)



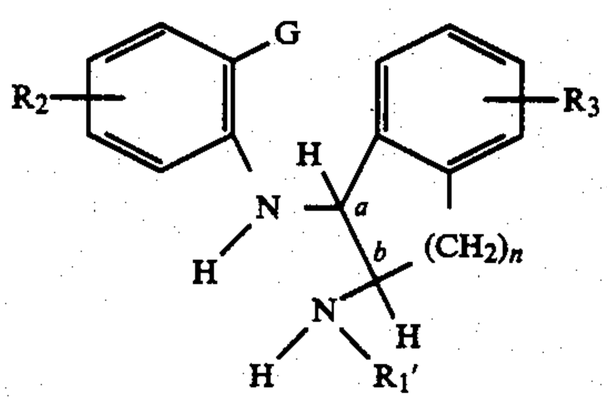
wherein R_1', R_2, R_3, n and the configuration of the C_a and C_b hydrogen atoms are as defined hereinbefore and one of X and Y is hydrogen and the other is hydroxyethyl, into a leaving group (L_9).

In the case of the aforementioned examples for the leaving group (L_9), the conversion may be carried out by reacting a compound of formula (XIV) with thionyl chloride, hydrogen bromide, mesyl or tosyl chloride.

The compound of formula (XIV) may in turn be prepared by reacting a compound of formula (X), as hereinbefore defined, with ethylene oxide in a solvent, such as ethanol, at, for example, room temperature. When R_1' is C_{1-4} alkoxycarbonyl, phenoxycarbonyl or benzyloxycarbonyl, the reaction occurs preferentially at the azepine nitrogen atom so that the major resulting compound of formula (XIV) is that wherein X is hydroxyethyl and Y is hydrogen. When, on the other hand, R_1' is R_1, the reaction occurs preferentially at the nitrogen atom attached to R_1 so that the major resulting compound of formula (XIV) is that wherein X is hydrogen and Y is hydroxyethyl.

The compounds of formulae (II) and (X) can both be prepared from a compound of formula (XV);

(XV)

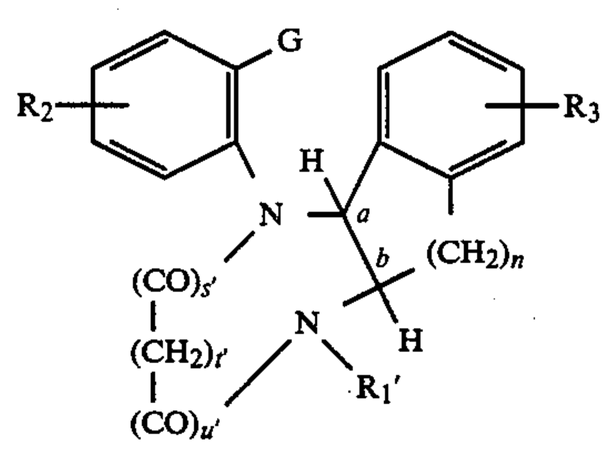


wherein R_1', R_2, R_3, n, G and the configuration of the C_a and C_b hydrogen atoms are as defined hereinbefore; (i) in the case of a compound of formula (II), by reaction with a compound of formula (XI), as defined hereinbefore, and, in the case where s or u is 1, reducing the carbonyl moiety to a methylene moiety; or (ii) in the case of a compound of formula (X), by cyclisation to form the azepine ring.

The reaction between the compounds of formulae (XV) and (XI) to give a compound of formula (II) may be carried out in a similar manner to the reaction between the compounds of formulae (X) and (XI), as described hereinbefore. When either of the leaving groups (L_7 and L_8) in a compound of formula (XI) is halo and s or u is 1 when G in formula (XV) is CH_2L_1, L_1 being hydroxy, there is a risk of a side-reaction between the compound of formula (XI) and the hydroxymethyl substituent in the compound of formula (XV). It is therefore preferred not to use this combination of

variables, for example, by using a compound of formula (XI), wherein s and u are 0, or by using another value for the leaving group (L_7 or L_8) or the leaving group (L_1). Alternatively, the hydroxymethyl substituent may be protected using a standard method and then the reaction with a compound of formula (XI) may be carried out and the resulting compound deprotected using a standard method.

When s or u is 1, the preparation proceeds through an intermediate of formula (XVI);



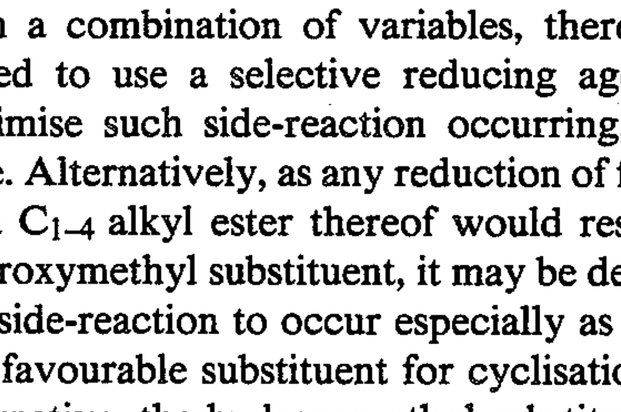
(XVI)

wherein R_1', R_2, R_3, n, G, the configuration of the C_a and C_b hydrogen atoms, s', t' and u' are as defined hereinbefore.

The reduction of the carbonyl moiety may be carried out in a similar manner to the reduction of the carbonyl moiety in an intermediate of formula (XII) although it is possible that G, when formyl, carboxy or a C_{1-4} alkyl ester thereof, may be reduced as a side-reaction. For such a combination of variables, therefore, it is preferred to use a selective reducing agent that would minimise such side-reaction occurring, such as diborane. Alternatively, as any reduction of formyl, carboxy or a C_{1-4} alkyl ester thereof would result mainly in a hydroxymethyl substituent, it may be desirable to allow the side-reaction to occur especially as hydroxymethyl is a favourable substituent for cyclisation. As a further alternative, the hydroxymethyl substituent may be oxidised back to formyl or carboxy using manganese dioxide or potassium permanganate and, if a C_{1-4} alkyl ester were required, esterifying the carboxy group so formed.

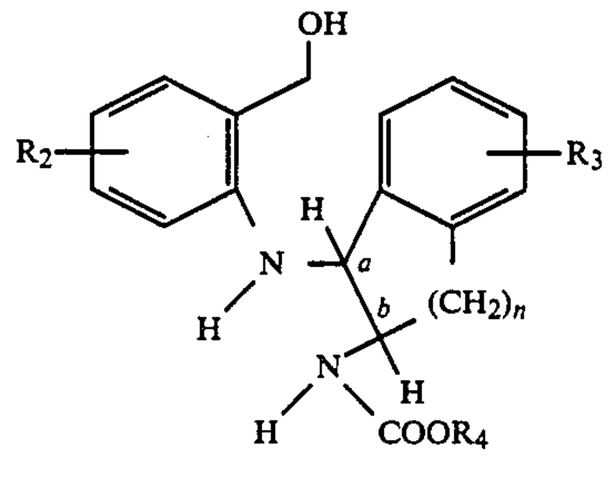
The cyclisation of a compound of formula (XV) to give a compound of formula (X) may be carried out in a similar manner to the cyclisation of a compound of formula (II).

The compound of formula (XV) may be prepared by reducing a compound of formula (XVII);



(XVII)

wherein R_2 to R_4, n and the configuration of the C_a and C_b hydrogen atoms are as defined hereinbefore and R_{11} is C_{1-4} alkyl; optionally converting the hydroxy group of the hydroxymethyl substituent in the resulting compound of formula (XVIII),



(XVIII)

wherein R_2 to R_4, n and the configuration of the C_a and C_b hydrogen atoms are as defined hereinbefore, into another leaving group (L_1), or optionally oxidising the hydroxymethyl substituent to formyl or carboxy and optionally esterifying a carboxy group so formed into a C_{1-4} alkyl ester thereof; and optionally converting the C_{1-4} alkoxycarbonyl, phenoxycarbonyl or benzyloxycarbonyl group into R_1.

In order not to reduce the C_{1-4} alkoxycarbonyl, phenoxycarbonyl or benzyloxycarbonyl group, the reduction of a compound of formula (XVII) is preferably carried out with lithium aluminium hydride at a low temperature or with lithium triethylborohydride.

The optional conversion of the hydroxy group of the hydroxymethyl substituent in the resulting compound of formula (XVIII) may be carried out conventionally. For example, the optional conversion of the hydroxy group into one of the other leaving groups (L_1), as defined hereinbefore, may be carried out with thionyl chloride (when L_1 is chloro), phosphorous tribromide (when L_1 is bromo), a C_{1-4} alcohol and acid (when L_1 is C_{1-4} alkoxy), mesyl or tosyl chloride (when L_1 is mesyl or tosyl), a C_{1-4} alkanoyl chloride or anhydride (when L_1 is C_{1-4} alkanoyloxy) and a C_{1-4} alkoxycarbonyl chloride (when L_1 is C_{1-4} alkoxycarbonyloxy).

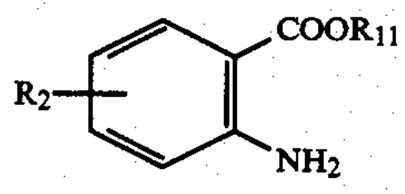
The optional oxidation of the hydroxymethyl substituent in a compound of formula (XVIII) into formyl, carboxy or a C_{1-4} alkyl ester thereof may be carried out by reaction with manganese dioxide (to give formyl), with potassium permanganate (to give carboxy) or with a mixture of manganese dioxide, sodium cyanide, acetic acid and a C_{1-4} alkanol (to give a C_{1-4} alkyl ester).

It is preferred however that no conversion of the hydroxy group or the hydroxymethyl substituent is carried out and that therefore the leaving group (L_1) is hydroxy.

The optional conversion of C_{1-4} alkoxycarbonyl, phenoxycarbonyl or benzyloxycarbonyl into R_1 may be carried out as described hereinbefore. In fact, in relation to the most preferred process of the present invention, namely the first process involving the cyclisation of a compound of formula (II), it is preferred that any such conversion is carried out at this stage providing of course that the resulting group (R_1) is not likely to interfere with the course of any subsequent reaction or to be affected by it. If, however, either is likely, then it is preferred to maintain the C_{1-4} alkoxycarbonyl, phenoxycarbonyl or benzyloxycarbonyl group until after the subsequent reactions have been carried out and then to carry out the required conversion. In the preferred case when, in a compound of formula (XV), G is CH_2L_1, L_1 being hydroxy, and R_1' is R_1 is methyl, it is particularly advantageous to prepare such compounds by reducing both ester functions in the corresponding compound of formula (XVII) in one operation. Thus,

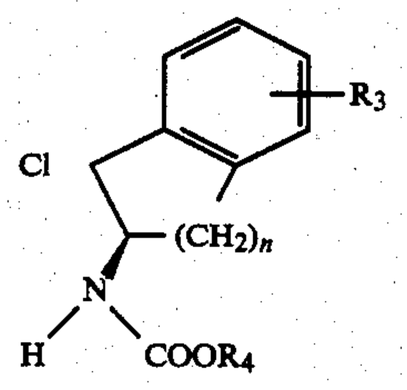
the $COOR_{11}$ ester function becomes hydroxymethyl and the $COOR_4$ ester function becomes methyl. A convenient reducing agent for such a reduction is lithium aluminium hydride, which is preferably used at room temperature or above in a solvent, such as diethyl ether.

The compound of formula (XVII) may be prepared by reacting a compound of formula (XIX);



(XIX)

wherein R_2 and R_{11} are as defined hereinbefore, with a compound of formula (XX);

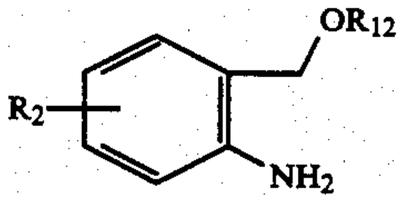


(XX)

wherein R_3, R_4 and n are as defined hereinbefore.

The reaction between the compounds of formulae (XIX), when R_2 is hydrogen, and (XX) is preferably carried out with an excess of the compound of formula (XIX) as solvent.

Alternatively although less preferred when R_2 is hydrogen, the compound of formula (XV) may be prepared by reacting a compound of formula (XXI);

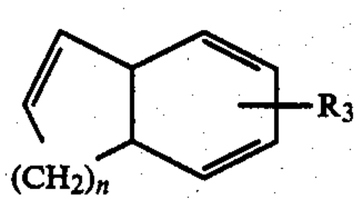


(XXI)

wherein R_2 is as defined hereinbefore and R_{12} is hydrogen or C_{1-4} alkyl, with a compound of formula (XX), as defined hereinbefore; in the case when R_{12} is hydrogen, optionally converting the hydroxy group of the hydroxymethyl substituent in the resulting compound of formula (XVIII), as defined hereinbefore, into another leaving group (L_1), or optionally oxidising the hydroxymethyl substituent to formyl or carboxy and optionally esterifying a carboxy group so formed into a C_{1-4} alkyl ester thereof; and optionally converting the C_{1-4} alkoxycarbonyl, phenoxycarbonyl or benzyloxycarbonyl into R_1.

The reaction between the compounds of formulae (XXI) and (XX) is preferably carried out in a solvent, such as dimethylformamide, in the presence of barium carbonate.

The compound of formula (XX) may be prepared by reacting a compound of formula (XXII);



(XXII)

wherein R_3 and n are as defined hereinbefore, with a compound of formula (XXIII);

(XXIII)

wherein R_4 is as defined hereinbefore.

The reaction between the compounds of formulae (XXII) and (XXIII) is preferably carried out in a solvent, such as toluene, at a temperature of 25° to 75° C.

The compound of formula (XXIII) is preferably prepared in situ by reacting a mixture of chlorine and a compound of formula (XXIV);

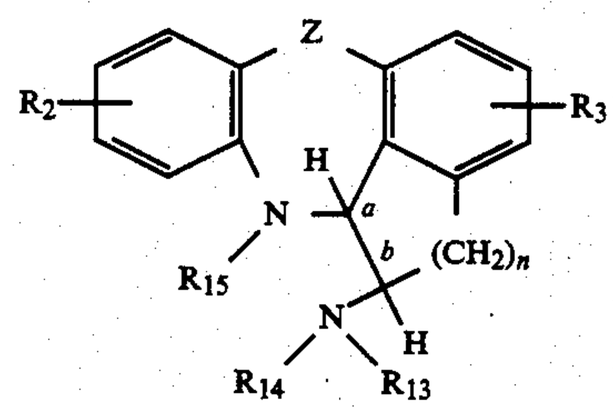
(XXIV)

wherein R_4 is as defined hereinbefore.

The reaction between the compound of formula (XXIV) and chlorine is preferably carried out in buffered aqueous solution.

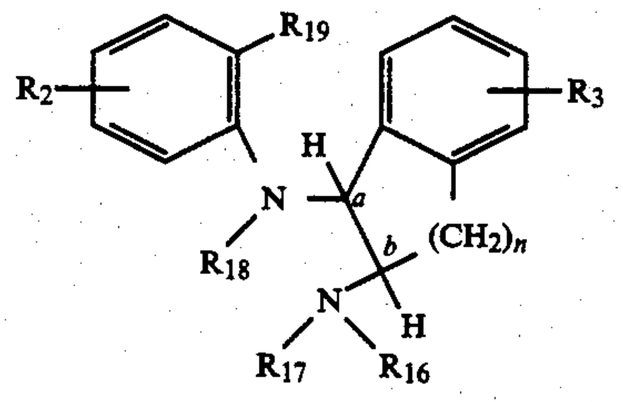
The compounds of formulae (XIX), (XXI), (XXII) and (XXIV) are known compounds or can be prepared in a manner similar to the preparation of known compounds.

The intermediates of formulae (II), (III), (IV), (IX), (X), (XII), (XIII), (XIV), (XV), (XVI), (XVII), and (XVIII) are novel intermediates and represent part of the present invention. Collectively they are of formulae (XXV) and (XXVI);



(XXV)

wherein R_2, R_3, n and the configuration of the C_a and C_b hydrogen atoms are as defined hereinbefore and either Z is methylene and either R_{13} is $COOR_4$ or R_{10}, R_4 and R_{10} being as defined hereinbefore, and R_{14} and R_{15} together are C_{1-3} alkylene, or R_{13} is R_1', as defined hereinbefore, and R_{14} and R_{15} are both hydrogen, or R_{14} is W, as defined hereinbefore, and R_{15} is V, as defined hereinbefore, or R_{14} is Y, as defined hereinbefore, and R_{15} is X, as defined hereinbefore, or R_{14} and R_{15} together are $(CO)_{s'}—(CH_2)_{t'}—(CO)_{u'}$, s', t' and u' being as defined hereinbefore, or Z is J, as hereinbefore defined, R_{13} is R_1', as hereinbefore defined, and R_{14} and R_{15} together are C_{1-3} alkylene; and



(XXVI)

wherein R_2, R_3, n and the configuration of the C_a and C_b hydrogen atoms are as defined hereinbefore and either R_{16} is R_1', as defined hereinbefore, and R_{17} and R_{18} are both hydrogen or together are either C_{1-3} alkylene or $(CO)_{s'}—(CH)_{t'}—(CO)_{u'}$, s', t' and u' being as defined hereinbefore, and R_{19} is G, as defined hereinbefore, or R_{16} is $COOR_4$, R_4 being as defined hereinbefore,

R_{17} and R_{18} are both hydrogen and R_{19} is $COOR_{11}$, R_{11} being as defined hereinbefore, or hydroxymethyl.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I), or an N-oxide or pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by a mixture, is usually adapted for oral or parenteral administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, or injectable or infusable solutions or suspensions. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention, or an N-oxide or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The dose of the compound used in the treatment of CNS disorders, such as depression or anxiety, will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 10.0 mg., for example 0.2 to 1 mg; and such unit doses may be administered more than once a day, for example two or three times a day, so that the total daily dosage is in the range of about 0.01 to 10 mg/kg; and such therapy may extend for a number of weeks or months.

The invention also provides a method of treatment of CNS disorders, in particular depression in mammals including humans, which comprises administering to the sufferer an anti-depressant effective amount of a compound of the invention, or an N-oxide or pharmaceutically acceptable salt thereof.

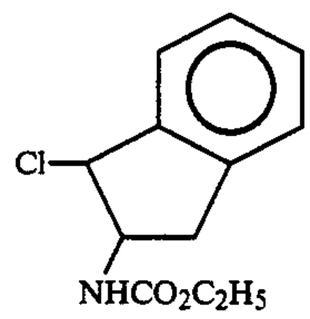
The invention further provides a compound of the invention, or an N-oxide or pharmaceutically acceptable salt thereof, for use in the treatment of CNS disorders in particular depression.

The following Examples illustrate the preparation of the compounds of the invention. The following Descriptions illustrate the preparation of intermediates to the compounds of the present invention. All temperatures are in degrees celsius and 'Rec' means recrystallised from.

DESCRIPTION 1

trans-1-Chloro-2-ethoxycarbonylaminoindane (D1)

(D1)

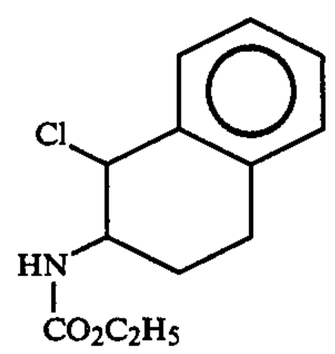


The title compound was prepared according to the procedure of B. J. Walker and P. J. Wrobel, J.C.S. Chem. Comm., 1980, 462 (85% yield; m.p. 82°–84°).

DESCRIPTION 2

trans-1-Chloro-2-ethoxycarbonylamino-1,2,3,4-tetrahydronaphthalene (D2)

(D2)

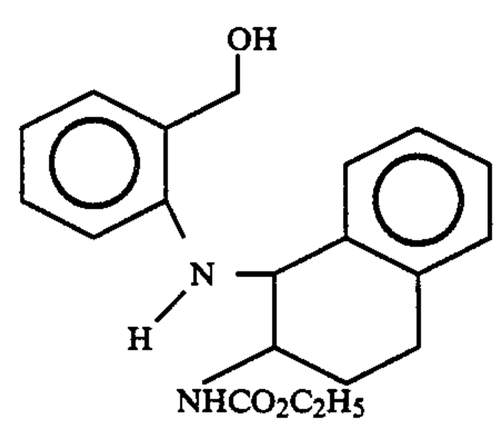


The title compound was prepared using a procedure similar to the one employed in Description 1 (74% yield; m.p. 124°–6°).

DESCRIPTION 3

trans-1-(2-Hydroxymethylanilino)-2-ethoxycarbonylamino-1,2,3,4-tetrahydronaphthalene (D3)

(D3)



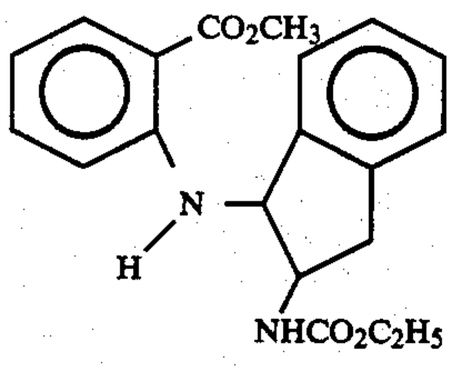
A solution of trans-1-chloro-2-ethoxycarbonylamino-1,2,3,4-tetrahydronaphthalene (12.8 g; 0.05 moles) and o-aminobenzyl alcohol (6.2 g; 0.05 moles) in dry dimethyl formamide (50 ml) was treated with finely ground barium carbonate (5.4 g; 0.0275 moles) and stirred under nitrogen at 85° for 10 h. The reaction mixture was diluted with water and extracted into ether. The combined organic layers were washed exhaustively with water, dried (Na_2SO_4) and concentrated in vacuo to give a light brown foam (15.6 g) which was purified on silica gel using 25% ethyl acetate in petroleum ether 60/80 as eluant. Pooling of pure fractions produced the title compound as a colourless

crystalline solid (6.1 g; 35%) m.p. 134°–5° (Rec. pentane/ether). Earlier fractions which were slightly contaminated with less polar impurity, afforded a further 1.4 g (8%) of the required product (m.p. 134°–5°) after recrystallisation from pentane/ether.

Nmr ($CDCl_3$): δ: 1.18 (3H,t,J=7), 1.5–2.5 (3H,m), 2.90 (2H,m), 4.04 (2H,q,J=7), 4.15 (1H,m), 4.57 (2H,s), 4.75 (2H, overlapping doublets), 6.65 (1H,m), 7.2 (6H,m).

DESCRIPTION 4

trans-1-(2-Methoxycarbonylanilino)-2-ethoxycarbonylaminoindane (D4)



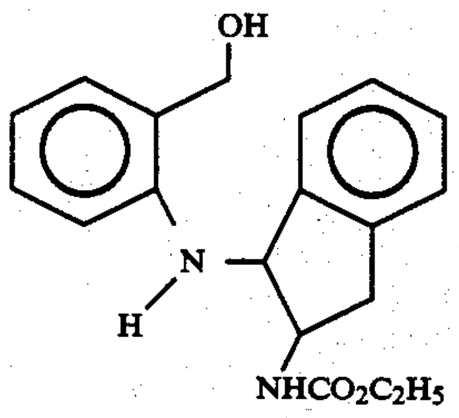
(D4)

trans-1-Chloro-2-ethoxycarbonylaminoindane (20 g, 0.084 moles) was treated with methyl anthranilate (60 ml) and stirred under nitrogen at 60° for 5 hr. The resulting viscous mixture was diluted with ether (500 ml), washed exhaustively with 2.5N HCl (8×250 ml), and then with saturated sodium bicarbonate followed by brine. After drying (Na_2SO_4) and concentration in vacuo a brown solid (25.7 g) was obtained. Crystallisation from pentane/ether afforded the title compound (14 g; 58%) m.p. 108°–110°. Concentration of mother liquors gave a less pure second crop (2.6 g).

Nmr ($CDCl_3$) δ: 1.21 (3H,t,J=7), 2.30 (1H,dd,J=16,6) 3.42 (1H,dd,J=16,7), 3.80 (3H,s), 3.9–4.5 (3H, m, overlapping signals), 4.92 (1H,d,J=5), 4.95 (2H, m, overlapping signals), 6.65 (1H, m), 7.26 (6H, m), 7.94 (1H,dd,J=9, 1.5).

DESCRIPTION 5

trans-1-(2-Hydroxymethylanilino)-2-ethoxycarbonylaminoindane (D5)



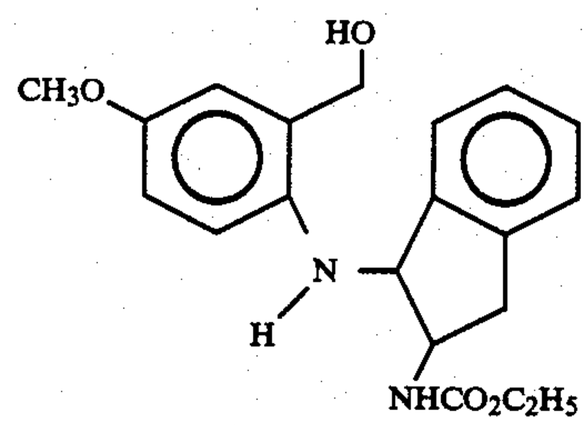
(D5)

A solution of the ester D4 (1.0 g, 2.8 mmoles) in dry tetrahydrofuran (6 ml) was cooled below −10° under nitrogen and treated dropwise with Super-hydride (Lithium triethylborohydride) (10 ml of a 1M Tetrahydrofuran solution). Stirring was continued overnight at room temperature. The reaction mixture was then cooled below 0° and treated with water (1 ml) followed by 5N HCl (25 ml). After stirring for 30 mins. the mixture was diluted with pentane. The aqueous layer was washed with ether (2×20 ml) basified (40% NaOH) and extracted into ether. The organic phase was washed (brine), dried (Na_2SO_4) and concentrated in vacuo to give the title compound as a colourless solid (0.75 g, 81%) m.p. 115°–7° (rec. ether/pentane).

Nmr ($CDCl_3$) δ: 1.17 (3H,t,J=7), 2.76 (1H,dd,J=16,8), 3.34 (1H,dd,J=16,8), 4.02 (2H,q, J=7), 4.35 (1H,m), 4.62 (2H,s), 4.82 (1H,d,J=7), 4.95 (1H,broad), 6.5–7.5 (8H,m).

DESCRIPTION 6

trans-1-(4-Methoxy-2-hydroxymethylanilino)-2-ethoxycarbonylaminoindane (D6)



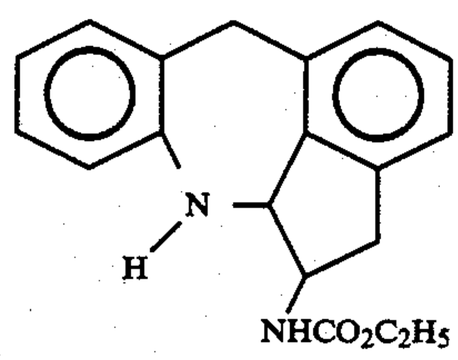
(D6)

A solution of 2-amino-5-methoxybenzyl alcohol (5 g; 32.7 m. mol) and trans-1-chloro-2-ethoxycarbonylaminoindane (7.83 g; 32.7 m.mol) in dimethylformamide (80 ml) was treated with barium carbonate (3.37 g; 17 m.mol) in a manner similar to that in Description 3 to give the title compound (5.1 g; 44%), m.p. 142°–144° (from ethyl acetate).

Nmr ($CDCl_3$) δ: 1.08(3H,t,$CO_2CH_2\underline{C}H_3$); 2.40–3.45 (2H,dd, 2×CH); 3.60(3H,s,OCH_3); 4.40(2H,s,$\underline{C}H_2OH$); 3.50–4.80(5H,m,$CO_2\underline{C}H_2$+N$\underline{H}\underline{C}\underline{H}$+OH); 5.47 (1H, d,8 Hz;$\underline{C}\underline{H}$); 6.40–7.40(7$\underline{H}$,m,aromatic $\underline{C}\underline{H}$).

DESCRIPTION 7

trans-1-Ethoxycarbonylamino-1,2,11,11a-tetrahydro-6H-benzo[f]indeno[1,7-bc]azepine (D7)



(D7)

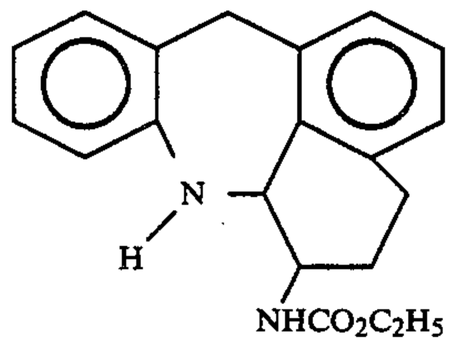
The alcohol prepared in Description 5 (8.6 g; 0.026 moles) was dissolved in methanesulphonic acid (86 g; 58 ml) and the cooled solution was treated with phosphorus pentoxide (17.2 g) and stirred at room temperature for 4 days. The mixture was poured onto ice, neutralised to pH7 (40% NaOH) and extracted into ether. The organic layers were washed (water), dried (Na_2SO_4) and concentrated in vacuo to give a yellow foam (6.4 g) containing two faster running products on tlc (Rf values 0.77 and 0.6-SiO_2/petroleum ether/ether-3/1). The mixture was separated on silica gel using 20% ethyl acetate in petroleum ether as eluant. The more polar component corresponded to the title compound and was isolated as a colourless crystalline solid (1.87 g; 23%).

Nmr ($CDCl_3$) δ: 1.28 (3H,t,J=7), 2,57 (1H,dd,J=16,10), 3.15 (1H,dd,J=16,8), 3.63 (1H,d,J=15), 4,25 (5H, overlapping signals), 4.68 (1H, d,J=8), 5.07 (1H, broad doublet), 6.5–7.3 (7H,m).

DESCRIPTION 8

trans-1-Ethoxycarbonylamino-1,2,3,7,12,12a-hexahydrobenzo[f]naphth[1,8-bc]azepine (D8)

(D8)



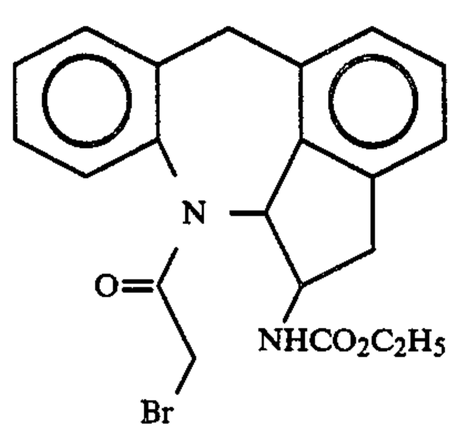
The title compound was prepared using a procedure analogous to the one outlined in Description 7 (21% yield).

Nmr ($CDCl_3$) δ: 1.25 (3H,t,J=7), 1.5–2.8 (2H,m), 2.85 (2H, m), 3.38 (1H,d,J=15), 3.75–4.90 (4H, overlapping signals), 4.85 (1H,d,J=15), 4.95 (1H,d,broad), 5.07 (1H,d,J=6), 6.35–7.4 (7H,m).

DESCRIPTION 9

trans-1-Ethoxycarbonylamino-11-bromoacetyl-1,2,11,11a-tetrahydro-6H-benzo[f]indeno[1,7-bc]azepine (D9)

(D9)



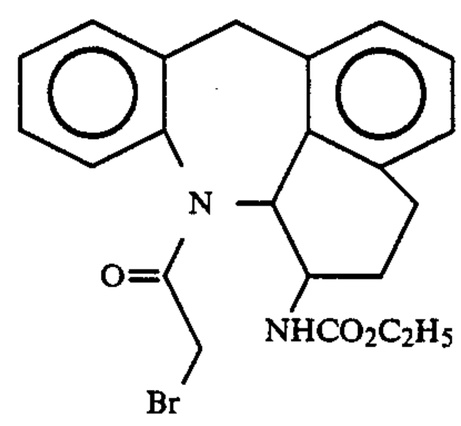
Bromoacetyl bromide (0.88 ml; 0.01 moles) was added dropwise to a solution of the amine prepared in Description 7 (3.08 g; 0.01 moles) in dry methylene chloride (25 ml) containing finely ground potassium carbonate (2.76 g; 0.02 moles) and cooled to 0°. Stirring was continued for 27 hours and during this period a further portion (0.2 ml) of bromoacetyl bromide was added. The mixture was then treated with water and after separation of the organic phase the aqueous layer was extracted with methylene chloride. The combined organic layers were washed (water), dried, (Na_2SO_4) and concentrated in vacuo to give a yellow solid. Purification by trituration with pentane/ether afforded the title compound as a colourless crystalline solid (4.1 g; 95%) m.p. 207.5°–210° C. (rec. ether).

Nmr ($CDCl_3$) δ: 1.33 (3H,t,J=7), 2.75 (1H,dd,H=15,10), 3.32 (1H,dd,J=16,8), 3.44 (1H,d,J=13), 3.80 (2H,s), 4.2 (4H,overlapping signals), 6.1 (2H,overlapping doublets) 6.8–7.5 (7H, m).

DESCRIPTION 10

trans-1-Ethoxycarbonylamino-12-bromoacetyl-1,2,3,7,12,12a-hexahydrobenzo[f]napth[1,8-bc]azepine (D10)

(D10)



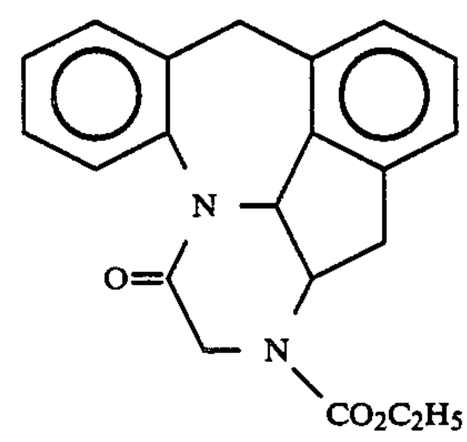
The title compound was prepared using a procedure similar to the one outlined in Description 9 (77% yield).

Nmr ($CDCl_3$) δ: 1,30 (3H,t,J=7), 2.0 (2H,m), 2,80 (2H,m), 3,44 (1H,d,J=14), 3,65 (1H,d,J=10), 3,72 (1H,d,J=10), 3,89 (1H,m), 4.19 (2H,q,J=7), 4,53 (1H,d,J=14), 5,54 (1H,d,J=9), 5,97 (1H,d,J=10), 6,97 (3H,m), 7,30 (4H,m).

DESCRIPTION 11

trans-10-Oxo-1,10,11,12,12a,12b-Hexahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]fluorene-12-carboxylic acid ethyl ester (D11)

(D11)



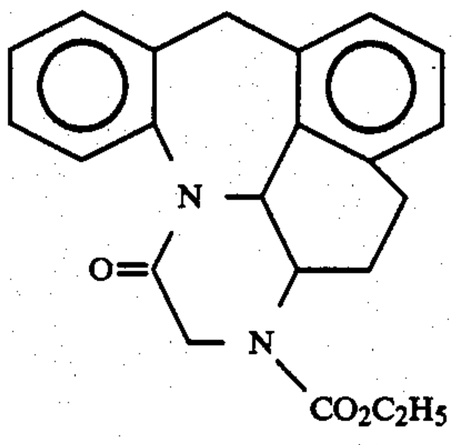
A solution of the urethane prepared in Description 9 (3.35 g; 7.8 mmoles) in dry dimethyl formamide (200 ml) was added over a period of 30 minutes to a stirred suspension of sodium hydride (0.26 g of 80% dispersion in oil; 8.6 mmoles) in the same dry solvent (20 ml) under nitrogen. Reaction temperature was maintained below 5° during addition and then allowed to rise to room temperature while stirring was continued for a further 3 h. The mixture was then carefully diluted with water and extracted into ether. The organic phase was washed exhaustively with water, dried (Na_2SO_4) and concentrated to give the title compound as a pale yellow solid (2.35 g; 90%) which was used without further purification.

Nmr ($CDCl_3$) δ: 1.35 (3H,t,J=7), 2.75 (1H,dd,J=16,10), 3,50 (1H,d,J=14), 3.55 (1H,dd,overlapping), 3.65–4.50 (4H,overlapping signals), 4.86 (1H,d,J=16), 5.35 (1H,d,J=11), 6.80–7.40 (6H,m), 7.60 (1H,m).

DESCRIPTION 12

trans-11-Oxo-1,2,6,11,12,13,13a,13b-octahydro-10b,13-diazabenzo[gh]pleiadene-13-carboxylic acid ethyl ester (D12)

(D12)



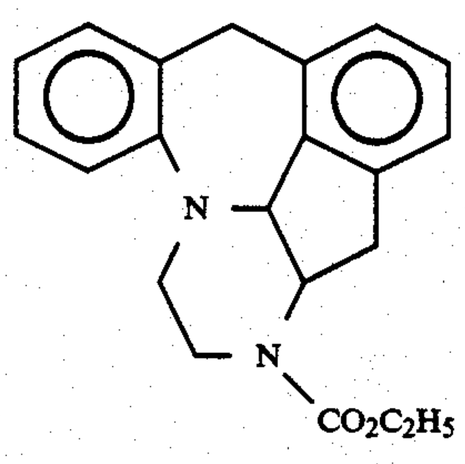
The title compound was prepared using the method outlined in Description 11 (yield 75%).

Nmr ($CDCl_3$) δ: 1.35 (3H,t,J=7), 2.85 (3H,m), 3.50 (2H,m), 3.80–4.50 (5H,overlapping signals), 4.95 (1H,d,J=16), 5.33(1H,d,J=11), 6.80–7.40 (7H,m).

DESCRIPTION 13

trans-1,10,11,12,12a,12b-Hexahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]fluorene-12-carboxylic acid ethyl ester (D13)

(D13)



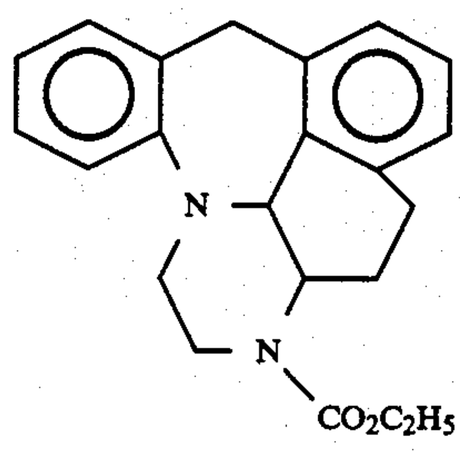
A solution of the urethane prepared in Description 11 (2.2 g; 6.3 mmoles) in dry tetrahydrofuran (15 ml) was added dropwise to 10.5 ml of 1M diborane in tetrahydrofuran cooled to ice temperature under nitrogen. The solution was then refluxed for 2 hours. After cooling to −10° the mixture was carefully acidified (5N HCl) and stirred for 30 mins. Solvent was removed in vacuo and the residue treated with 2N NaOH before extraction into ether. The dried (Na_2SO_4) organic phase was concentrated in vacuo to give a foam (1.9 g). Purification on silica gel using 15% ethyl acetate in petroleum ether 60/80 as eluant afforded the title compound as a colourless foam (1.45 g; 70%).

Nmr ($CDCl_3$) δ: 1.32 (3H,t,J=7), 3.0–4.7 (12H,m), 6.6–7.3 (7H,m).

DESCRIPTION 14

trans-1,2,6,11,12,13,13a,13b-Octahydro-10b,13-diazabenzo[gh]pleiadene-13-carboxylic acid ethyl ester (D14)

(D14)



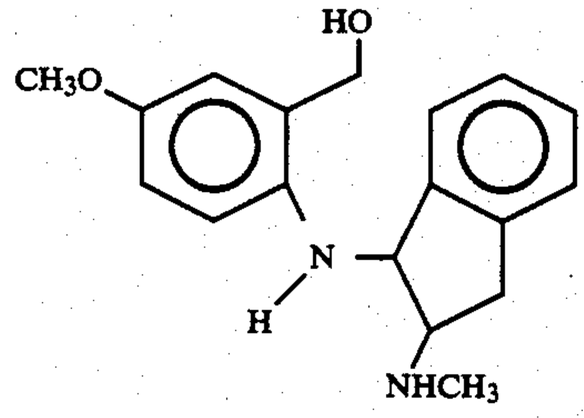
The title compound was prepared using a method similar to the one outlined in Description 13.

Nmr ($CDCl_3$) δ: 1.20 (3H,t,J=7), 1.50–2.50 (2H,m), 2.75 (2H,m), 3.25–4,40 (9H,m,overlapping signals), 4.52 (1H,d,J=13), 7.0 (7H,m).

DESCRIPTION 15

trans-1-(4-Methoxy-2-hydroxymethylanilino)-2-methylaminoindane (D15)

(D15)

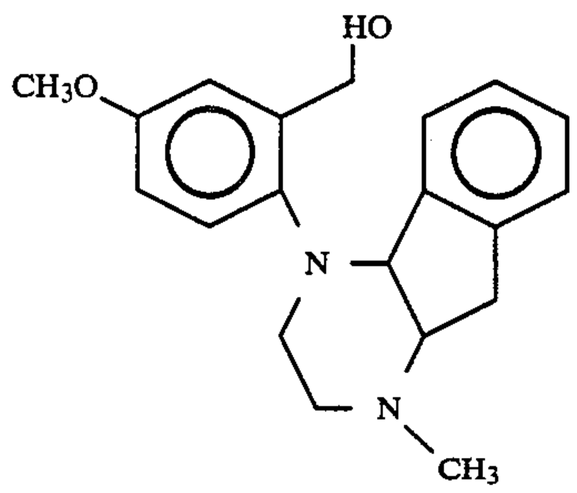


A solution of the carbamate prepared in Description 6 (4.00 g; 11.23 m.mol) in dry tetrahydrofuran (20 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (1.0 g; 26.3 m.mol) in dry ether (10 ml), under a nitrogen atmosphere, at 0°. The mixture was allowed to warm to room temperature and stirring continued for 2 days. The excess of hydride was decomposed as described in Example Ia and work-up gave a brown gum (2.66 g). Chromatography on Kieselgel 60 (100 g) in ethyl acetate containing increasing amounts of methanol gave the title compound as a pale gum (1.086 g; 33%).

Nmr ($CDCl_3$) δ: 2.37(3H,s,NCH_3); 2.50–3.90(6H,br,CH_2+CH+2×NH+OH); 3.64(3H,s,OCH_3); 4.47(2H,s,$\underline{C}H_2OH$); 4.50–4.78(1H,d,CH); 6.54–6.85 and 7.05–7.30 (7H,m,aromatic CH).

DESCRIPTION 16

trans-4-(4-Methoxy-2-hydroxymethylphenyl)-1-methyl-2,3,4,4a,9,9a-hexahydro-1H-indeno[1,2-b]pyrazine (D16)



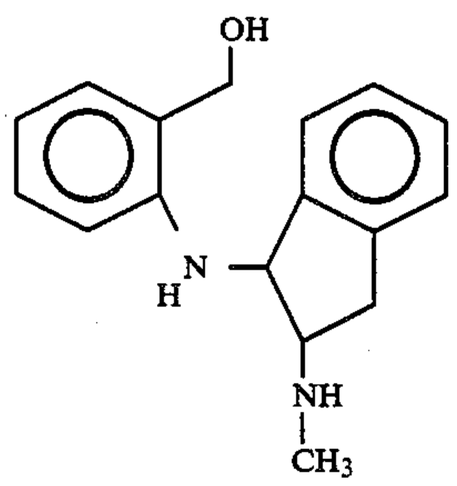
(D16)

A solution of the diamine prepared in Description 15 (880 mg; 2.95 m.mol) and dry triethylamine (2 ml) in dibromoethane (6 ml) was added dropwise, over 30 min, to dibromoethane (10 ml) at 100° with stirring, under a nitrogen atmosphere. After 1 hr, triethylamine (2 ml) was added and stirring continued for a further 1 hr at 100°. The mixture was allowed to cool to room temperature and then partitioned between dilute sodium hydroxide (200 ml) and chloroform (200 ml). The organic phase was washed with water (2×100 ml), saturated brine (50 ml) and dried (K_2CO_3). Evaporation in vacuo gave a buff solid (0.8 g) which was recrystallised from chloroform-ether to give the title compound as off-white crystals (478 mg; 50%), m.p. 179°–183°.

Nmr ($CDCl_3$): δ: 2.35–3.25 (8H,m,3×CH_2+CH+OH), 2.40 (3H,s,NCH_3), 3.83(3H,s,OCH_3), 4.20(1H,d J9 Hz,CH), 4.50–5.00(2-H,ABq, J13 Hz,$\underline{CH_2}OH$), 6.15(1H,dJ8 Hz,CH), 6.75–7.45 (6H,m,aromatic).

DESCRIPTION 17

trans-1-(2-Hydroxymethylanilino)-2-methylaminoindane (D17)



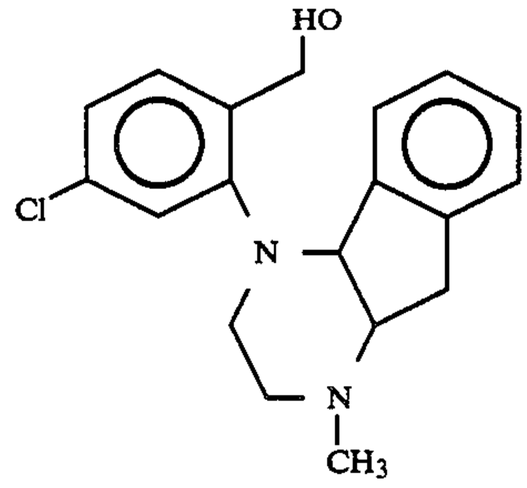
(D17)

A solution of trans 1-(2-methoxycarbonylanilino)-2-ethoxycarbonylaminoindane (1.73 kg; 4.9 moles) in diethyl ether (36 l) was added dropwise to a suspension of lithium aluminium hydride (900 g; 23.7 moles) in diethyl ether (28 l), under nitrogen, over a period of ca 1.5 h. After stirring overnight at room temperature the excess lithium aluminium hydride was carefully decomposed with water (2.5 l), and 10% sodium hydroxide (30 l) and water (5 l) was added. The organic layer was separated and the aqueous phase extracted with two further portions of ether (2×20 l). The combined extracts were washed (water), dried ($MgSO_4$) and concentrated. Crystallisation from ethyl acetate/pet. ether afforded the title compound (1.17 Kg; 89%) m.p. 113°–4°.

Nmr ($CDCl_3$) δ: 2.2 (2H, brs, exchanges with D_2O), 2.45 (3H,s), 2.5–3.5 (3H, overlapping signals), 4.6 (2H,s), 4.8 (1H, t, J=8), 5.07 (1H, d, J=8, exchanges with D_2O), 6.5–7.5 (8H,m).

DESCRIPTION 18

trans-4-(5-Chloro-2-hydroxymethylphenyl)-1-methyl-2,3,4,4a,9,9a-hexahydro-1H-indeno[1,2-b]pyrazine (D18)



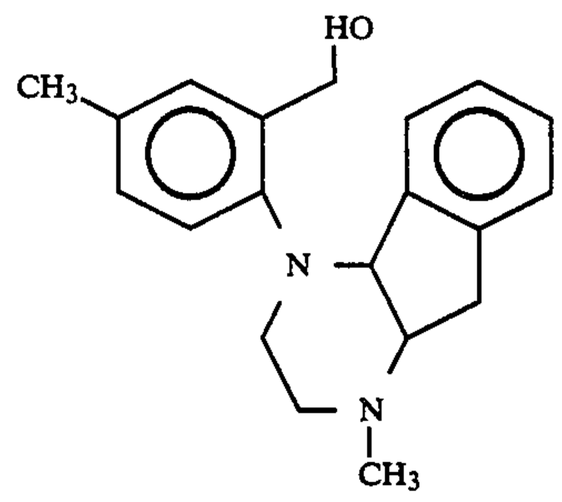
(D18)

The title compound was prepared in a manner similar to that in Description 16.

Nmr ($CDCl_3$) δ: 2.35 (3H,s,NCH_3), 2.40–3.40 (7H, overlapping signals), 4.18 (1H,d,J9 Hz), 4.40–5.00 (2H, ABq, J13 Hz, $\underline{CH_2}OH$) 6.10 (1H,d, J7 Hz, aromatic CH) 6.60–7.40 (6H,m,aromatic CH).

DESCRIPTION 19

trans-4-(2-Hydroxymethyl-4-methylphenyl)-1-methyl-2,3,4,4a,9,9a-hexahydro-1H-indeno[1,2-b]pyrazine (D19)



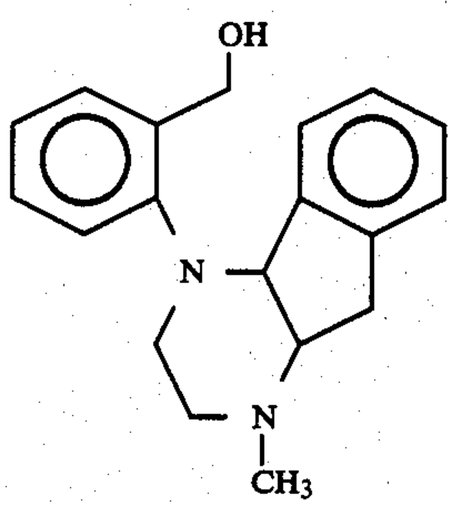
(D19)

The title compound was prepared in a manner similar to that in Description 16.

Nmr ($CDCl_3$) δ: 2.34 and 2.38 (2×3H,s, 2×CH_3), 2.30–3.25 (7H,overlapping signals), 4.17 (1H,d,J9 Hz, CH), 4.25–5.20 (3H,m,CH_2OH), 6.10 (1H,d, J7 Hz, aromatic CH), 6.53–7.25 (6H,m, aromatic CH).

DESCRIPTION 20

trans-4-(2-Hydroxymethylphenyl)-1-methyl-2,3,4,4a,9-,9a-hexahydro-1H-indeno[1,2-b]pyrazine (D20)



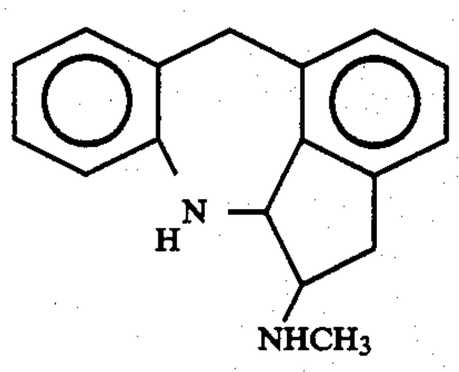
(D20)

A solution of trans 1-(2-hydroxymethylanilino)-2-methylaminoindane (1.16 kg; 4.3 moles) in 1,2-dibromoethane (7 l, 17.1 moles) and triethylamine (2.5 l; 34 moles) was added dropwise to stirred 1,2-dibromoethane (13 l; 31.9 moles) at ca. 100° over a period of 1.5 h. This was followed by triethylamine (2.5 l; 34 moles) added dropwise over 30 min. The reaction was cooled to 50° and diethyl ether (80 l) was added with good stirring. After stirring for 1 h the precipitated triethylammonium bromide was filtered off and the resulting solution concentrated in vacuo to ca 3.5 l. Addition of ethyl acetate (2.5 l) assisted crystallisation of the required product. Filtration and trituration (pet. ether) afforded the title compound as a white crystalline solid (687 g; 54%) m.p. 166–7°.

Nmr ($CDCl_3$) δ: 2.3–3.4 (10H, overlapping signals), 4.3 (1H,d,J=9), 4.62 (1H,d,J=13), 4.9 (1H,brs, exchange with D_2O), 5.0 (1H,d,J=13), 6.15 (1H,d,J=8), 6.7–7.6(7H,m).

DESCRIPTION 21

trans-1-Methylamino-1,2,11,11a-tetrahydro-6H-benzo[f]indeno[1,7-bc]azepine (D21)



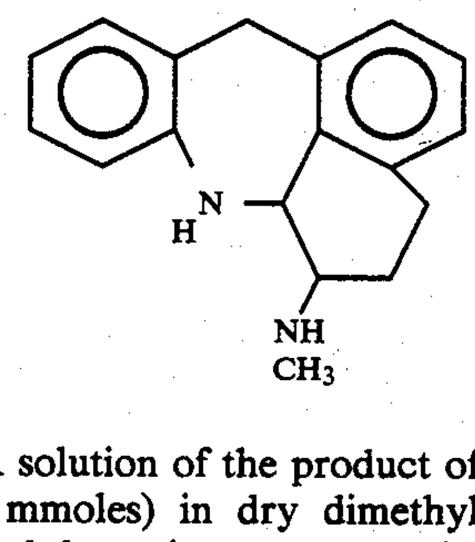
(D21)

A solution of the product of Description 7 (1.16 g; 3.76 mmoles) in dry tetrahydrofuran (20 ml) was added to a stirred suspension of lithium aluminium hydride (0.42 g; 11.0 mmoles) in the same dry solvent (20 ml) under nitrogen. The mixture was refluxed for 1 h. After treatment with wet ether followed by careful addition of water the precipitate was filtered off and the filtrate concentrated to give the title compound as a dark oil (0.80 g; 85%). Maleate salt m.p. 182°–4° (Rec. acetone/ether).

Nmr ($CDCl_3$) δ: 2.2–2.7 (2H, m, overlapping signals), 2.6 (3H, s), 3.0–3.5 (2H, m), 3.75 (1H, d, J=16), 4.3 (1H, d, J=16), 4.50 (1H, d, J=9), 6.6–7.3 (7H, m).

DESCRIPTION 22

trans-1-Methylamino-1,2,3,7,12,12a-hexahydrobenzo[f-]naphth[1,8-bc]azepine (D22)



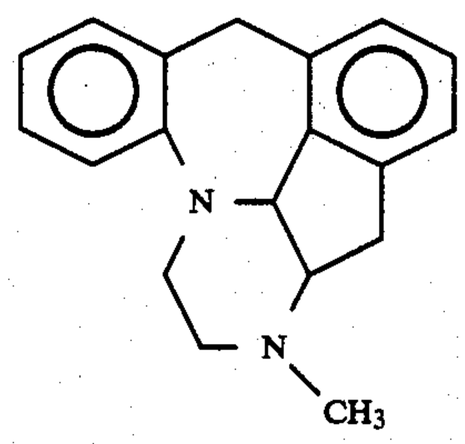
(D22)

A solution of the product of Description 8 (644 mg; 2.0 mmoles) in dry dimethylformamide (4 ml) was added dropwise to a suspension of sodium hydride (66 mg of an 80% dispersion in oil; 2.2 mmoles) in the same dry solvent (1 ml) cooled to 0° under nitrogen. After 12 min methyl iodide (0.14 ml; 2.2 mmoles) was added and the mixture was stirred for a further 30 min. The reaction was then diluted with water and extracted into ether. The organic phase was washed exhaustively with water, dried (Na_2SO_4) and concentrated to give trans-1-(N-ethoxycarbonyl-N-methylamino)-1,2,3,7,12,12a-hexahydrobenzo[f]napth[1,8-bc]azepine as a yellow foam (0.64 g; 96%). A solution of this product (0.57 g; 1.7 mmoles) in ethanol (25 ml) was treated with sodium hydroxide (8 ml of a 40% aqueous solution) and the mixture refluxed under nitrogen for 26 h. Solvent was removed in vacuo and the residue was diluted with water and extracted into ether. Further purification by extraction into 2N HCl followed by neutralisation and back extractions into ether afforded the title compound as a yellow gum (0.30 g; 67%) which crystallised on standing.

Nmr ($CDCl_3$) δ: 1.5–2.8 (2H,m), 2.55 (3H,s), 2.75 (5H,m), 3.40 (1H,d,J=15), 4.82 (1H,d,J=15), 4.96 (1H,d,J=5), 6.3–7.3 (7H,m). Treatment with D_2O resulted in exchange of two protons in the multiplet at δ3.75.

EXAMPLE Ia

trans-12-Methyl-1,10,11,12,12a,12b-hexahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]fluorene (E1)



(E1)

A solution of the urethane prepared in Description 13 (1.4 g; 4.0 mmoles) in dry tetrahydrofuran (10 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.45 g; 12.0 mmoles) in the same dry solvent (4 ml) under nitrogen, and the mixture was refluxed for 50 mins. Excess hydride was destroyed with wet ether and after careful treatment with water the precipitate of aluminium oxides was filtered off and

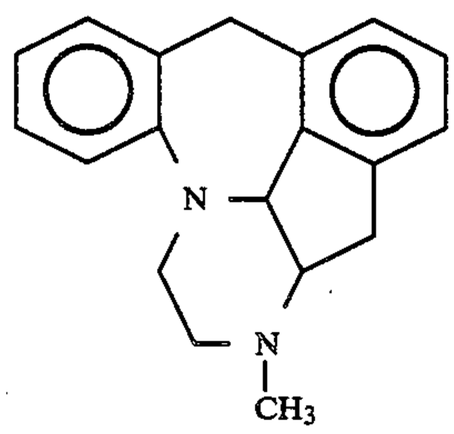
the filtrate concentrated in vacuo to give the title compound as a light yellow foam (0.98 g; 89%) which crystallised on addition of acetone.m.p. 151°–2° (from pentane/ethyl acetate).

Nmr δ: 2.20 (1H,ddd,J=10,10,6), 2.35 (3H,s), 2.50 (1H,ddd,J=12,12,3), 2.61 (1H,dd,J=14,11), 2.87 (1H,m), 2.88 (1H,dd,J=14,6), 3.45 (1H,d,J=13), 3.69 (1H,ddd,J=14.5,11,3), 3.87 (1H,ddd,J=14,3,3), 4.37 (1H,d,J=13), 4.48 (1H,d,J=10), 6.7–7.3 (7H,m).

Treatment of the free base with 1 equivalent of maleic acid in acetone solution afforded the maleate salt. m.p. 183°–5° (from acetone/ether).

	C	H	N
Found	70.32	6.25	7.01
$C_{23}H_{24}N_2O_4$ Requires	70.39	6.16	7.14

EXAMPLE Ib (Alternative Procedure)



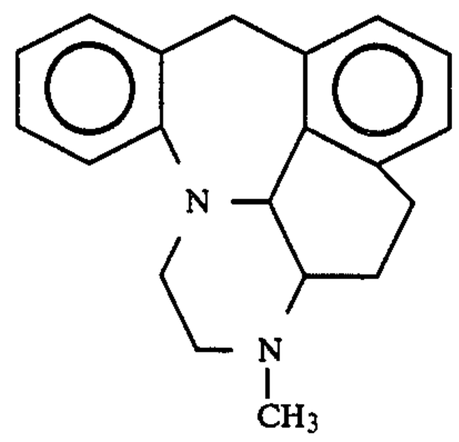
(EI)

trans-4-(2-Hydroxymethylphenyl)-1-methyl-2,3,4,4a,9,9a-hexahydro-1H-indeno[1,2-b]pyrazine (680 g; 2.31 moles) was added to stirring orthophosphoric acid (6.8 l of an 88% solution) at ca 90°. After 1 h the mixture was poured onto a mixture of ice (20 kg) and chloroform (12.5 l) and stirred vigorously as 40% sodium hydroxide solution was carefully added to neutralise the acid while the temperature was maintained below 45°. The organic layer was separated and the aqueous phase extracted with two further portions of chloroform. The combined chloroform layers were washed (water), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash chromatography, using pet. ether/acetone (70/30) as eluant, followed by crystallisation afforded the title compound as a colourless solid (560 g; 88%). m.p. 151°–2° (Rec twice pentane/ethyl acetate).

	C	H	N
Found	82.43	7.27	10.30
$C_{19}H_{20}N_2$ Requires	82.57	7.29	10.13

EXAMPLE II

trans-13-methyl-1,2,6,11,12,13,13a,13b-octahydro-10b,13-diazabenzo[gh]pleiadene (EII)



(EII)

Title compound was prepared from the urethane of Description 14 in a manner analogous to the procedure outlined in Example 1a.

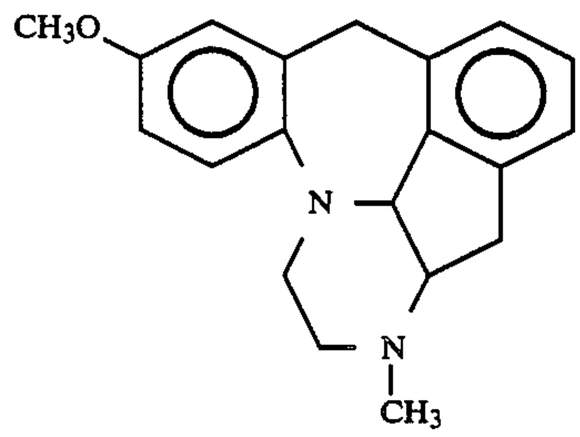
Nmr ($CDCl_3$) δ: 1.50–4.0 (14H overlapping signals) 4.90 (1H,d,J=13), 7.1 (7H,m).

Maleate Salt—m.p. 116°–7°.

	C	H	N
Found	70.49	6.45	6.72
$C_{24}H_{26}N_2O_4$ Requires:	70.92	6.45	6.89

EXAMPLE III

trans-7-Methoxy-12-methyl-1,10,11,12,12a,12b-hexahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]-fluorene (EIII)



(EIII)

The alcohol prepared in Description 16 (450 mg; 1.39 m.mol) in orthophosphoric acid (6 ml) was stirred at 95° for 8 h and then allowed to cool to room temperature. The mixture was poured into water (200 ml), basified with 40% sodium hydroxide solution and extracted with chloroform (2×150 ml). The combined extracts were dried (K_2CO_3) and evaporation in vacuo gave a brown gum. Chromatography on Kieselgel 60 (10 g) in 10% methanol-ethyl acetate gave the title compound as a gum (276 mg, 65%), which solidified on standing.

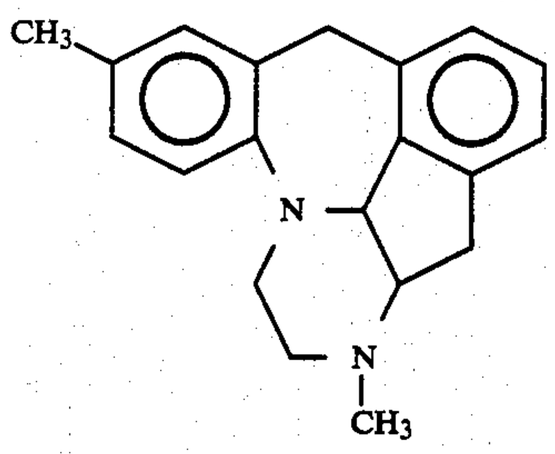
Nmr ($CDCl_3$) δ: 2.36(3H,s,NCH_3), 3.45(1H,d,J13 Hz,bridgehead CH), 3.74 (3H,s,OCH_3), 4.33(1H,d,J13 Hz,bridgehead CH).

A portion (250 mg) of the above was converted into a monomaleate salt (200 mg), m.p. 208.5°–210° (from methanol-ether).

	C	H	N
Found:	68.03	6.16	6.70
$C_{24}H_{26}N_2O_5$ Requires:	68.23	6.20	6.63

EXAMPLE IV

trans-7,12-Dimethyl-1,10,11,12,12a,12b-hexahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]fluorene (EIV)



(EIV)

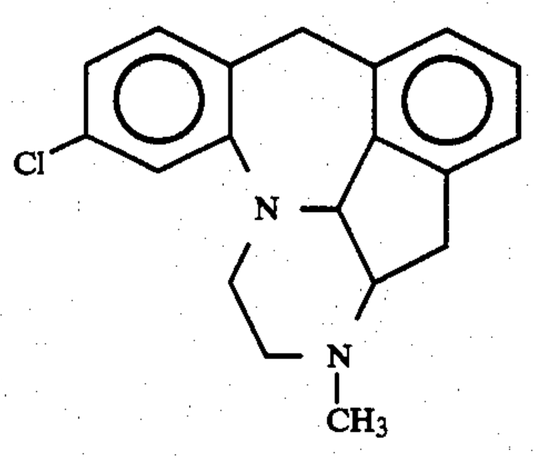
The title compound was prepared from the alcohol of Description 19 in a similar manner to Example III and converted into a maleate salt m.p. 207°–211° (dec) (from acetone).

	C	H	N
Found	70.45	6.32	6.84
$C_{24}H_{26}N_2O_4$ Requres:	70.92	6.45	6.89

Nmr (d_6DMSO) δ: 2.18 (3H,s,CH_3), 2.85 (3H,s,NCH_3), 6.97 and 7.15 (2×3H,s,aromatic CH).

EXAMPLE V

trans-8-Chloro-12-methyl-1,10,11,12,12a,12b-hexahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]-fluorene (EV)



(EV)

The title compound was prepared from the alcohol of Description 18 in a similar manner to Example III.

Nmr ($CDCl_3$) δ: 2.30–3.10 (6H, overlapping signals), 2.34 (3H,s,NCH_3), 3.37 (1H,d,J14 Hz, bridgehead CH), 3.53–3.85 (1H,m,CH), 4.26 (1H,d,J14 Hz, bridgehead CH), 4.45 (1H,d,J9 Hz,CH), 6.50–7.15 (6H,m,aromatic CH).

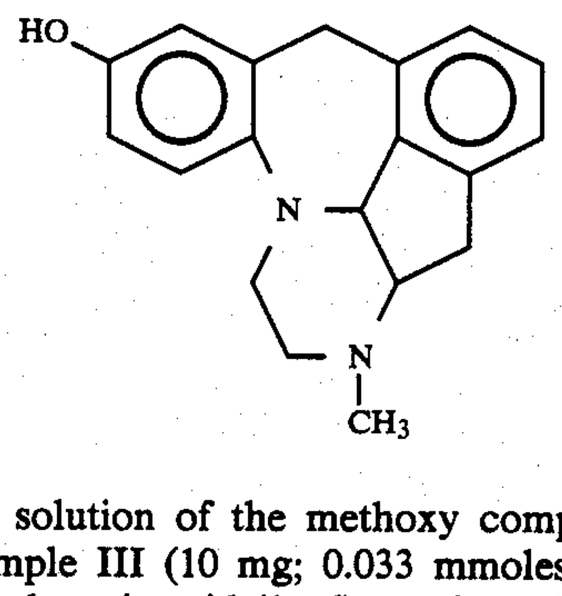
Found M+: 310.1242.

$C_{19}H_{19}N_2Cl$ requires 310.1237.

A portion of the title compound was converted into a maleate salt, m.p. 195°–197° (from acetone).

EXAMPLE VI

trans-7-Hydroxy-12-methyl-1,10,11,12,12a,12b-hexahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]-fluorene (EVI)



(EVI)

A solution of the methoxy compound prepared in Example III (10 mg; 0.033 mmoles) in 47% aqueous hydrobromic acid (1 ml) was heated under reflux for 5 hr and then allowed to cool to room temperature. The mixture was diluted with water (20 ml), made basic (pH about 14) with 40% sodium hydroxide solution and extracted with chloroform. The pH of the aqueous layer was adjusted to 7 with conc. hydrochloric acid and extraction with chloroform (2×20 ml) removed the product. The extracts were dried ($MgSO_4$) and evaporation in vacuo gave a brown gum which was fractionated by preparative layer chromatography on silica using 10% methanol-ethyl acetate to develop the plates. The band at Rf 0.47 afforded the title compound as a pale yellow gum (3 mg; 32%) which solidified on standing.

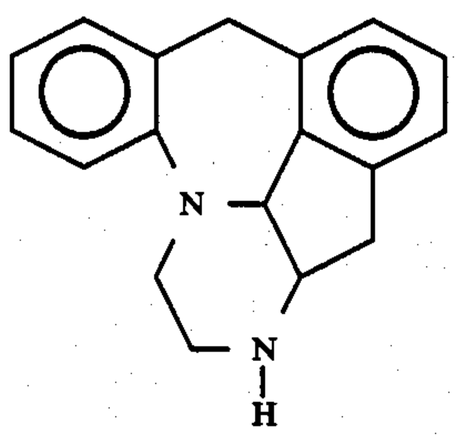
Nmr ($CDCl_3$) δ: 2.00–3.00 (6H,m,$(CH_2)_2$+CH+OH); 2.35 (3H,s,NCH_3); 3.43(1H,d,J14 Hz, CH bridgehead); 3.55–3.80(2H,m,CH_2); 4.15–4.45(2H,m,CH bridgehead+NCH); 6.55–7.15 (6H,m, aromatic)

Found M+ 292.1572.

$C_{19}H_{20}N_2O$ requires 292.1576.

EXAMPLE VII

trans-1,10,11,12,12a,12b-Hexahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]fluorene (EVII)



(EVII)

The product obtained in Example I (13.8 g; 0.05 moles) in dry toluene (150 ml) was treated with ethyl chloroformate (48 ml, 0.50 moles) and the mixture refluxed for 7 h. After concentration in vacuo excess reagent was removed by azeotropic distillation with several portions of toluene. The residue was partitioned between water and ether, and the aqueous layer extracted with two further portions of ether. The combined organic layers were washed (brine), dried (Na_2SO_4) and concentrated to give a crude foam (17 g) containing the required trans-1,10,11,12,12a,12b-hex-

ahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]fluorene-12-carboxylic acid ethyl ester. A solution of this product in ethanol (300 ml) was treated with sodium hydroxide (50 ml of a 40% aqueous solution) and refluxed under nitrogen for 6 h. After concentration in vacuo the reaction mixture was diluted with water and extracted into ether. The organic phase was washed (brine), dried (Na_2SO_4) and concentrated to a dark foam. Chromatographic separation on silica using 30% methanol in ethyl acetate as eluant afforded the title compound as an off-white solid (3.8 g; 30%) m.p. 132.5°–135° (Rec. ethyl acetate/petroleum ether 60/80).

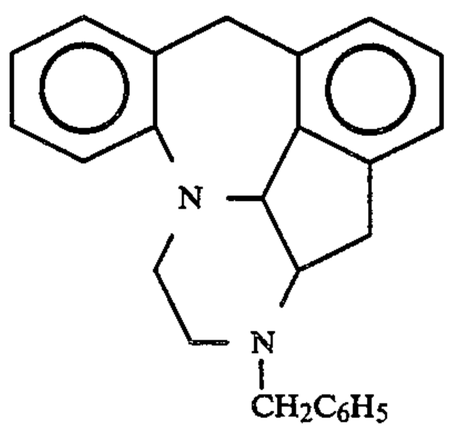
Nmr ($CDCl_3$) δ: 2.5–4.0 (9H,m,overlapping signals), 4.32 (1H,d,J=13), 4.39 (1H,d,J=10), 6.6–7.3 (7H,m).

	C	H	N
Found	82.38	6.92	10.53
$C_{18}H_{18}N_2$ Requires	82.41	6.92	10.67

EXAMPLE VIII

trans-12-Benzyl-1,10,11,12,12a,12b-hexahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]fluorene (EVIII)

(EVIII)



A solution of the product of Example VII (500 mg; 1.90 m moles) in acetone (25 ml) containing benzyl bromide (0.25 ml; 2.1 m moles) and potassium carbonate (290 mg; 2.1 m moles) was stirred at room temperature for 6 h. After concentration in vacuo the residue was treated with water and extracted into ether. The organic phase was washed (brine), dried (Na_2SO_4) and concentrated. Purification on silica gel using ethyl acetate as eluant afforded the title compound as a colourless solid (0.55 g; 82%).

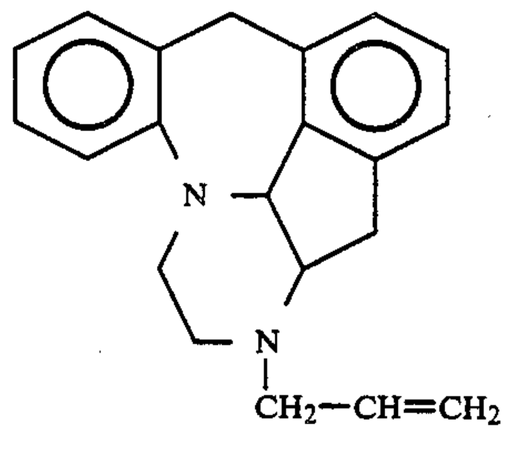
Nmr ($CDCl_3$) δ: 2.1–3.0 (5H,m,overlapping signals), 3.16 (1H, d, J=13), 3.45 (1H, d, J=13), 3.7 (2H, m, overlapping signals), 4.0 (1H, d, J=13), 4.2–4.65 (2H, overlapping doublets), 6.6–7.6 (12H,m).

Treatment of the free base with one equivalent of maleic acid in acetone solution afforded the maleate salt. m.p. 212°–5° (dec) (Rec. acetone).

EXAMPLE IX

trans-12-(Prop-2-enyl)-1,10,11,12,12a,12b-hexahydro-5H-9b,12-diaza-benzo[5,6]cyclohepta[1,2,3,4-def]fluorene (EIX)

(EIX)



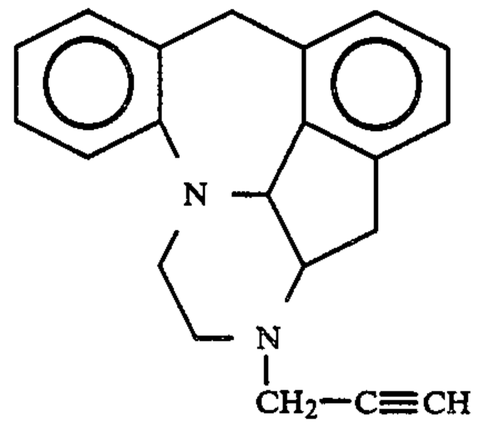
The title compound was prepared by treatment of trans-1,10,11,12,12a,12b-hexahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]fluorene with allyl bromide using a procedure similar to the one outlined in Example VIII. Maleate salt m.p. 187°–190° (dec).

Nmr ($CDCl_3$) δ: 2.1–3.1 (6H,m), 3.45 (1H,d,J=13), 3.55–3.90 (3H,m), 4.4 (1H,d,J=13), 4.5 (1H,d,J=9), 5.25–5.35 (2H,m), 5.75–6.25 (1H,m), 6.65–7.35 (7H,m).

EXAMPLE X

trans-12-(Prop-2-ynyl)-1,10,11,12,12a,12b-hexahydro-5H-9b,12-diazabenzo-[5,6]cyclohepta[1,2,3,4-def]fluorene (EX)

(EX)



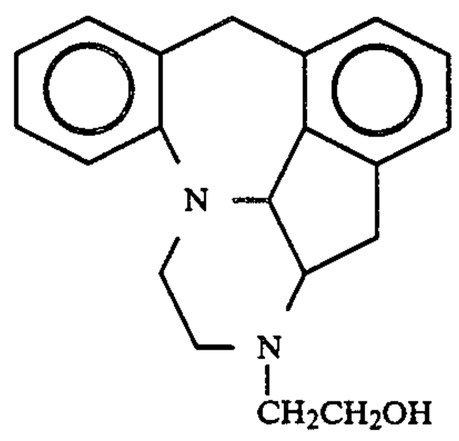
The title compound was prepared by treatment of trans-1,10,11,12,12a,12b-hexahydro-5H-9b, 12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]fluorene with propargyl bromide using a procedure similar to one outlined in Example VIII. Maleate salt m.p. 165°–70°.

Nmr ($CDCl_3$) δ: 2.0–2.95 (6H,m), 3.35–3.90 (5H,m), 4.35 (1H,d,J=14), 4.50 (1H,d,J=8), 6.65–7.25 (7H,m).

EXAMPLE XI

trans-12-(2-Hydroxyethyl)-1,10,11,12,12a,12b-hexahydro
5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]fluorene (EXI)

(EXI)



A solution of the product of Example VII (0.5 g; 1.90 m moles) in methanol (30 ml) containing potassium carbonate (0.26 g; 1.90 m moles) was treated with ethylene oxide as a gas for several minutes, and stirred overnight at room temperature. After concentration in vacuo, the residue was treated with water and extracted into ether. The organic phase was dried (Na_2SO_4) and solvent removed in vacuo. Purification on silica gel using diethyl ether as eluant, progressively increasing the polarity by adding up to 30% ethyl acetate, afforded the title compound as a cream solid (0.35 g; 60%).

Nmr ($CDCl_3$) δ: 2.0–3.1 (8H, m), 3.45 (1H,d,J=14), 3.6–3.85 (4H,m), 4.35 (1H,d,J=14), 4.45 (1H,d,J=10), 6.7–7.4 (7H,m).

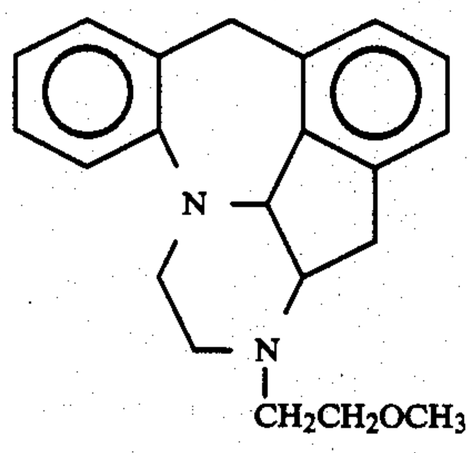
Treatment of the free base with 1 equivalent of maleic acid in acetone gave the maleate salt, m.p. 175°–7°.

	Analysis		
	C	H	N
Found:	68.13	6.14	6.69
$C_{20}H_{22}N_2O$ Requires:	68.23	6.20	6.63

EXAMPLE XII

trans-12-(2-Methoxyethyl)-1,10,11,12,12a,12b-hexahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]-fluorene (EXII)

(EXII)



A solution of the product of Example VII (0.5 g; 190 m moles) in pyridine (3 ml) was cooled in an ice bath and treated with methoxyacetyl chloride (0.4 ml; 4.38 m moles). After stirring at room temperature for 0.5 h the reaction mixture was treated with water and extracted into ether. The organic phase was washed once with 1M hydrochloric acid, dried (Na_2SO_4), and concentrated in vacuo. Purification on silica gel using diethyl ether as eluant afforded the required trans-12-(methoxyacetyl)-1,10,11,12,12a,12b-hexahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def] fluorene as a brown solid (0.35 g; 55%). A solution of this compound (0.35 g; 1.05 m moles) in dry tetrahydrofuran (15 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (0.125 g; 3.2 m moles) in the same dry solvent (5 ml) under nitrogen, and the mixture was refluxed for 3 h. Excess hydride was destroyed with wet ether and, after careful treatment with water, the precipitate of aluminium oxides was filtered off and the filtrate concentrated in vacuo. Purification on silica gel using 50% ethyl acetate in diethyl ether as eluant afforded the title compound as a brown oil (0.26 g; 78%).

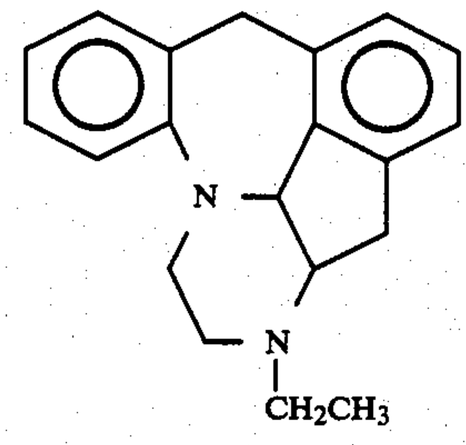
Nmr ($CDCl_3$) δ: 2.1–3.1 (7H,m), 3.35 (3H,s), 3.45–3.95 (5H,m), 4.33 (1H,d,J=14), 4.48 (1H,d,J=10), 6.6–7.3 (7H,m).

Treatment of the free base with 1 equivalent of maleic acid in acetone solution gave the maleate salt, m.p. 170°–2°.

EXAMPLE XIII

trans-12-Ethyl-1,10,11,12,12a,12b-hexahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]fluorene (EXIII)

(EXIII)



A solution of the product of Example VII (0.5 g; 1.90 m moles) in dry dichloromethane (8 ml) was cooled in an ice-bath and treated with acetic anhydride (0.233 g; 2.3 m moles) in one portion. After stirring at room temperature for 0.5 h the reaction mixture was treated with water and extracted into dichloromethane. The organic phase was dried (Na_2SO_4) and solvent removed in vacuo. Purification on silica gel using diethyl ether as eluant afforded the required trans-12-acetyl-1,10,11,12,12a,12b-hexahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]fluorene as a white solid (0.54 g; 93%).

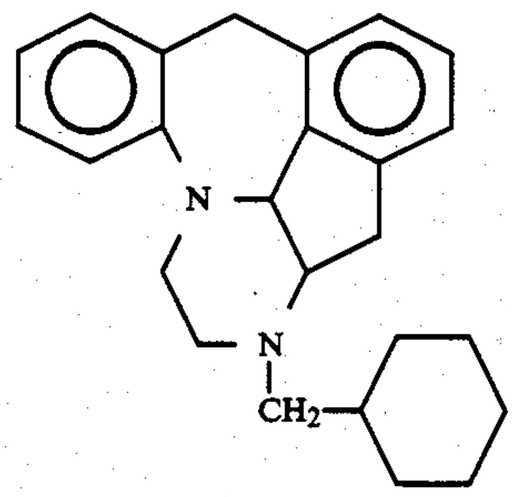
This compound was reduced according to the method of Example XII, to give the title compound and the maleate salt prepared similarly, m.p. 188°–9° (dec.).

Nmr ($CDCl_3$) δ: 1.15 (3H,t,J=8), 2.05–3.10 (7H, m, overlapping peaks), 3.45 (1H,d,J=14), 3.60–4.05 (2H,m), 4.375 (1H,d,J=14), 4.50 (1H,d,J=8), 6.65–7.35 (7H, m, overlapping peaks).

EXAMPLE XIV

trans-12-Cyclohexylmethyl-1,10,11,12,12a,12b-hexahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]-fluorene (EXIV)

(EXIV)



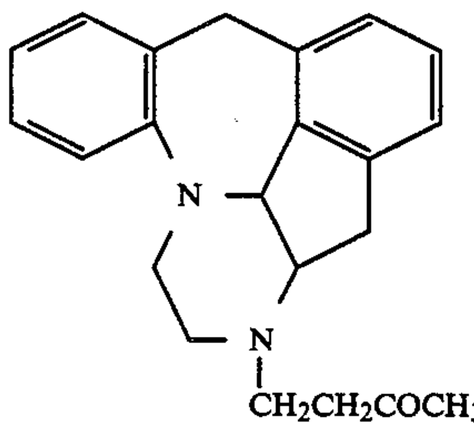
The title compound was prepared according to the method of Example XII. Maleate salt m.p. 197°–9° (dec.).

Nmr ($CDCl_3$) δ: 0.65–3.0 (18H,m, overlapping signals), 3.6–3.9 (3H,m), 4.3 (1H,d,J=14), 4.4 (1H,d,J=10), 6.6–7.4 (7H,m).

EXAMPLE XV

trans-12-(3-Oxobutyl)-1,10,11,12,12a,12b-hexahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]fluorene (EXV)

(EXV)



A solution of the product of Example VII (0.5 g; 1.90 m moles) in 1,4-dioxan (40 ml) was treated with methyl vinyl ketone (0.23 ml; 2.8 m mol) and stirred at 100° under nitrogen for 15 h. Concentration in vacuo followed by purification of the residue on silica gel using 50% ethyl acetate 60°–80° petroleum ether afforded the title compound as a beige solid (0.48 g; 76%).

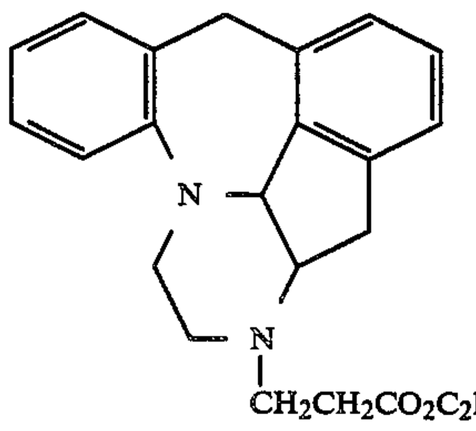
Nmr ($CDCl_3$) δ: 2.20 (3H,s), 2.40–3.00 (9H,m, overlapping signals), 3.42 (1H,d,J=14), 3.50–3.80 (2H,m), 4.33 (1H,d,J=14), 4.44 (1H,d,J=10), 6.75–7.25 (7H,m).

Treatment of the free base with 1 equivalent of maleic acid in acetone gave the maleate salt, m.p. 148°–50°.

EXAMPLE XVI

trans-12-(2-Ethoxycarbonylethyl)-1,10,11,12,12a,12b-hexahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]fluorene (EXVI)

(EXVI)



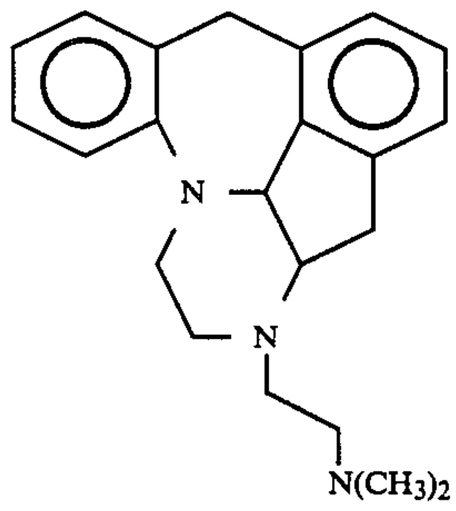
The title compound was prepared from ethyl acrylate according to the method of Example XV. Maleate salt m.p. 178°–183° (dec).

Nmr ($CDCl_3$) δ: 1.28 (3H,t,J=8), 2.1–3.2 (9H,m, overlapping signals), 3.30–3.85 (3H,m), 3.90–4.50 (4H,m), 6.65–7.25 (7H,m).

EXAMPLE XVII

trans-12-(2[1]-dimethylaminoethyl)-1,10,11,12,12a,12b-hexahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]fluorene (EXVII)

(EXVII)



A solution of the product of Example VII (0.50 g; 1.91 mmoles) in dry methylene chloride (10 ml) containing anhydrous potassium carbonate (0.29 g) was cooled in ice and treated dropwise with bromoacetyl bromide (0.183 ml; 2.1 mmoles). The reaction was allowed to warm to room temperature. After 1 h the reaction mixture was diluted with methylene chloride and washed with water. Drying (Na_2SO_4) followed by concentration in vacuo afforded trans-12-(bromoacetyl)-1,10,11,12,12a,12b-hexahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]fluorene as a light brown foam (0.73 g). This material was dissolved in a mixture of ethanol (50 ml) and 1,4-dioxan (25 ml) and treated with dimethylamine (5 ml of 33% w/w solution in industrial methylated spirits). After 0.5 h the solvent was removed in vacuo, and trituration of the residue with ether afforded an off white solid characterised as trans-12-(dimethylaminoacetyl)-1,10,11,12,12a,12b-diazabenzo[5,6]**cyclohepta**[1,2,3,4-def]fluorene. Refluxing this product in dry tetrahydrofuran (100 ml) with lithium aluminium hydride (0.21 g; 5.7 mmoles) for 2 h afforded the title compound as a light brown oil (0.45 g; 70%).

Nmr ($CDCl_3$) δ: 2.30 (6H,s), 2.30–3.15 (9H,m, overlapping signals), 3.43 (1H,d,J=13), 3.55–3.90 (2H,m), 4.35 (1H,d,J=13), 4.50 (1H,d,J=9), 6.6–7.3 (7H,m).

PHARMACOLOGY

Compounds of the invention inhibit the behavioural symptoms induced by 5-methoxy-N,N-dimethyltryptamine (5-MDMT), a central 5-hydroxytryptamine agonist, and are central 5HT antagonists. As such they would be expected to possess antidepressant (Ogren, S O, Fuxe, K, Agnati, L F, Gustafsson J A, Jonsson, G, and Holm A C, 1979, J Neural Trans, 46, 85–103) and-/or anxiolytic (Stein, L, Kline, D, and Bellugi, J D, 1975, in Advances in Biochemical Psychopharmacology, ed Costa, E, and Greengard, P, Vol 14, 29–44, Raven Press, NY) activity.

METHOD

Mice (♂ CD-1 Charles River) are pretreated with the compounds (10 animals/group) under investigation and 1 h later are injected with 10 mg/kg i.p. 5-methoxy-N,N-dimethyltryptamine (Sigma). The symptoms of fore-paw tapping movements, head jerks and splayed limbs are scored: 1, present; 0, absent, giving a maximum score of 3/mouse or 30/group. Results are expressed as the percentage inhibition compared to the group treated with 5-methoxy-N,N-dimethyltryptamine

alone. The dose of compound inhibiting the symptoms by 50% is determined graphically. The results are shown in Table 1.

TOXICITY

No toxic effects were observed in the above tests.

TABLE 1

Compound	ED_{50} mg/kg (p.o.)
trans-12-Methyl-1,10,11,12,12a,12b,-hexahydro-5H—9b,12-diazabenzo[5,6] cyclohepta[1,2,3,4,-def]fluorene (Example 1)	8

BIOCHEMISTRY

Blockade of presynaptic α_2-adrenoceptors on noradrenegic neurones effects an increase in intrasynaptic noradrenaline, and thus in the central nervous system could be expected to have an antidepressant effect.

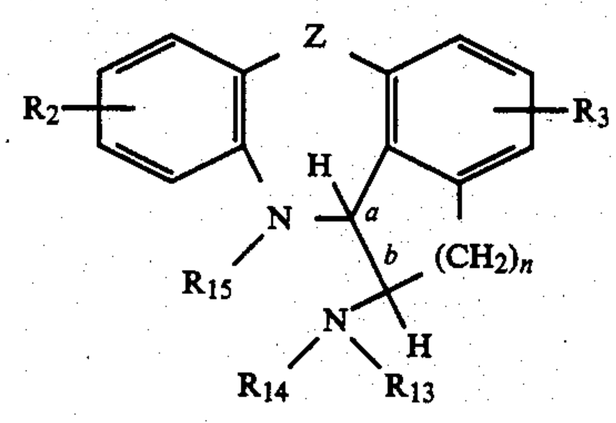
[^{3}H]-Clonidine binds to α_2-adrenoceptor sites and inhibition of this binding correlates with the blockade of α_2-adrenoceptors. In vitro inhibition by some of the present compounds of the binding of [^{3}H]-clonidine to isolated rat-brain synaptic membrane fragments was therefore determined to provide an indication of antidepressant activity. This was carried out using standard biochemical binding study techniques, by the method of Maggi et al, Eur. J. Pharm. 1980, 61, 91. IC_{50} values were obtained from log [dose] against % inhibition curves; Ki values were determined using the Cheng-Prusoff equation. The results are shown in Table 2.

TABLE 2

Compound	Ki (nm)
trans-12-Methyl-1,10,11,12,12a,12b-hexahydro-5H—9b,12-diazabenzo[5,6] cyclohepta[1,2,3,4-def]fluorene (Example I)	88
trans-13-Methyl-1,2,6,11,12,13,13a, 13b-octahydro-10b,13-diazabenzo [gh]pleiadene (Example II)	169

What we claim is:

1. A compound of formula (XXV):



(XXV)

wherein R_2 and R_3 are the same or different and are hydrogen, hydroxy, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkylthio, halogen, or trifluoromethyl, and n is 1 or 2, the hydrogen atom bonded to the C_a carbon atom being trans to the hydrogen atom bonded to the C_b carbon atom and either:

(I) Z is methylene; and

R_{13} is $COOR_4$ or R_{10}, R_4 being C_{1-4} alkyl, phenyl or benzyl and R_{10} being C_{1-4} alkyl substituted by halogen or halocarbonyl or, C_{1-4} alkylcarbonyl, C_{3-7} cycloalkylcarbonyl, C_{3-7} cycloalkyl C_{1-3} alkylcarbonyl or halo C_{1-4} alkylcarbonyl, and R_{14} and R_{15} together are C_{1-3} alkylene, or

R_{13} is hydrogen, C_{1-7} alkyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl or C_{1-4} alkyl substituted by C_{2-7} alkenyl, C_{2-7} alkynyl, C_{3-7} cycloalkyl, hydroxy, thiol, C_{1-4} alkoxy, C_{1-4} alkylthio, carboxy, C_{1-4} alkoxycarbonyl, C_{1-4} alkanoyl, amino optionally substituted by one or two C_{1-4} alkyl or by C_{4-6} polymethylene optionally containing an oxygen or nitrogen atom, amino carbonyl optionally N-substituted by one or two C_{1-4} alkyl, or benzoyl or phenyl either being optionally ring-substituted by C_{1-4} alkyl, C_{1-4} alkoxy, halogen or trifluoromethyl or C_{1-4} alkoxycarbonyl, phenoxycarbonyl or benzyloxycarbonyl, and R_{14} and R_{15} are both hydrogen, or R_{14} is W and R_{15} is V, wherein one of V and W is hydrogen and the other is (CH_2) L_9, L_9 being a leaving group, or one of R_{14} and R_{15} is hydrogen and the other is hydroxylethyl, or R_{14} and R_{15} together are $(CO)_{s'}—(CH_2)_{t'}—(CO)_{u'}$, wherein s' and u' are 0 and t' is 0 to 3 such that s'+t'+u' is 1 to 3, with proviso that at least one of s' and u' is 1; or

(II) Z is CO or CHOH; and

R_{13} is as defined above, and R_{14} and R_{15} together are C_{1-3} alkylene.

2. A compound according to claim **1**, selected from the group consisting of: trans-1-ethoxycarbonylamino-1,2,11,11a-tetrahydro-6H-benzo[f]indeno[1,7-bc]azepine; trans-1-ethoxycarbonylamino-1,2,3,7,12,12a-hexahydrobenzo[f]naphth[1,8-bc]azepine; trans-10-oxo-1,10,11,12,12a,12b-hexahydro-5H-9b,12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]fluorene-12-carboxylic acid ethyl ester; trans-11-oxo-1,2,6,11,12,13,13a, 13b-octahydro-10b, 13-diazabenzo[gh]pleiadene-13-carboxylic acid ethyl ester; trans-1,10,11,12,12a,12b-hexahydro-5H-9b, 12-diazabenzo[5,6]cyclohepta[1,2,3,4-def]fluorene-12-carboxylic acid ethyl ester; trans-1,2,6,11,12,13,13a,13b-octahydro-10b,13-diazabenzo[gh]pleiadene-13-carboxylic acid ethyl ester; trans-1-methylamino-1,2,11,11a-tetrahydro-6H-benzo[f]indeno[1,7-bc]azepine; and trans-1-methylamino-1,2,3,7,12,12a-hexahydrobenzo[f]naphth[1,8-bc]azepine.

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